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Jonathan L. Benumof, MD, *Consulting Editor*

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HEMORRHAGIC DISORDERS

Bruce D. Spiess, MD, *Guest Editor*

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Foreword

Anesthesiologists administer more than 60% of the blood products transfused in the United States, which accounts for approximately 2.5 million units of blood transfused each year. This is an enormous transfusion practice, and for any individual patient a transfusion can have important immediate and/or late implications that reach far beyond just the specialty of anesthesia. Patients' lives can be immediately saved (from hemorrhage), jeopardized (by developing a coagulopathy, a mismatch reaction), or chronically affected (by long-lasting infection—hepatitis has long been the number one infectious disease transmitted by blood transfusion). The much more recent acquired immunodeficiency syndrome (AIDS) crisis, however, has caused much public fear, which in turn, has resulted in pressure to put transfusion practices under intense review and rapid change when appropriate.

A number of these transfusion practice changes are destined to improve the management of hemorrhagic disorders in the operating room. For example, new research is increasing our understanding of oxygen supply and delivery and clearly indicates that the "trigger" to transfuse should no longer be a predetermined arbitrary number of 10 grams of hemoglobin per deciliter. Indeed, these studies have inspired recent National Institutes of Health (NIH) consensus conferences on blood product use; the findings and policy statements from these NIH conferences should be recognized by all practitioners. As an example of the changing practice of transfusion, new studies have made monitoring coagulation function in the operating room an online endeavor. Clearly, this type of improvement in the management of hemorrhagic disorders in the operating room will enable anesthesiologists to anesthetize severely ill patients better for more difficult operations (e.g., liver transplantation) than they could in the past. For all of these reasons, a contemporary, in-depth examination of transfusion and hemorrhage therapy in the operating rooms of the 1990s is a timely and essential contribution to the anesthesia literature; this issue of *Anesthesiology Clinics of North America* is such a contribution.

Anesthesiology Clinics of North America is fortunate to have Dr. Bruce Spiess guest edit this issue. Dr. Spiess has long had an interest in blood transfusion and physiology. His past and present participation in liver transplantations has enabled him to do high quality original studies on coagulation monitoring during that procedure, and his extensive publications on this subject have led to the wide application of these monitoring procedures to the management of hemorrhagic disorders in all operating rooms. He also has published extensively on the artificial blood substitutes, the perfluorocarbon emulsions. Dr. Spiess has pioneered a new anesthesiologist–blood bank cooperative program to assist in the collection of autologous blood from high-risk donors, thereby allowing a significantly larger segment of the population to benefit from autologous transfusion. Not surprisingly, he formerly served on the Rush-Presbyterian-St. Luke's Medical Center's transfusion committee and is a member of the American Society of Anesthesiologists Committee on Transfusion Medicine. Finally, because of Dr. Spiess's central position in transfusion practice, he has been able to choose contributors who are all nationally and/or internationally recognized in the areas of anemia, hemorrhage, and blood product use. In summary, Dr. Spiess's broad expertise with clinical transfusion medicine makes him eminently qualified to guest edit this important issue on hemorrhagic disorders.

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Preface

Bruce D. Spiess, MD
Guest Editor

At the beginning of the 1980s, anesthesia practices were considered quite sophisticated. Hemodynamic monitoring, pulmonary artery catheterization, and ventilatory critical care medicine were modern advances in anesthesiology's clinical armamentarium. Blood transfusions were a routine part of that advanced practice; however, their use was not always critically scrutinized. Ten years ago (and today), 60% of blood transfusions (red cell) were administered in the perioperative period. Historically, patients were required to possess a "magic" 10 or more grams of hemoglobin per deciliter before general anesthesia or surgery. Therefore, preoperative blood transfusions were seen as a necessary practice that were often required to ensure a smooth and successful outcome. At that time, the health care providers concerned with patient transfusion viewed blood as a scarce resource in heavy demand. Efforts were made constantly to ensure the blood supply. Transmission of hepatitis was a known risk of transfusion, but that risk was never a sufficiently compelling problem to dispel the magic of the number 10. How many patients spent extra days in the hospital, and how many contracted communicable diseases as a result of those practices? How many millions of health care dollars were spent to satisfy a widely held belief that transfusions were frequently necessary?

Today, however, physicians are highly cognizant of the fact that homologous blood transfusions can have a detrimental effect on the health of a patient. Therefore, the rule requiring an arbitrary level of hemoglobin before anesthetization is no longer de rigueur. The change in transfusion practice is one example of how contemporary "truths" and practices may, in the future, become fallacious and unacceptable. The 10-g hemoglobin level is one example of a clinical dinosaur in operative transfusion medicine. Trigger points indicating when to transfuse, when to use fresh frozen plasma, platelets, or homologous blood all have evolved into a considerably different practice today when compared with that of 10 years ago. The articles in this issue discuss these ever-changing trends in transfusion therapy.

Thoughtful introspection by anesthesiologists has been applied to the evaluation of preoperative laboratory tests, to the use of invasive monitoring, and most recently, to transfusion practices. While these self-examinations have, at times, been painful and have sparked many scientific debates, such debates are essential to ensure the safe use of our technologies and transfused blood. Because 60% of transfusions administered in the United States are performed in the perioperative period, it is essential that anesthesiologists spend time reviewing the motivations and clinical forces controlling the science of blood transfusions in the operating room. Their understanding and applied knowledge will have direct impact not only upon an individual patient's care but also upon health care economics in general, and ultimately, upon national public health.

Beginning 10 years ago, recognition of the epidemic proportions of acquired immunodeficiency syndrome (AIDS) gradually grew in the medical community. Fear of AIDS has resulted in profound pressure by patients upon their physicians to change transfusion practices. The operating room environment has in no way been isolated from that external pressure. Homologous transfusion has become, or will become shortly, an act of last resort. Research has focused on finding sources of *safe* blood and blood products that are not subject to the uncertainties involved in the use of blood taken from homologous blood donors. New technologies have been developed to harvest, wash, and process blood shed intraoperatively for re-use with the same patient. Use of euvolemic hemodilution and autologous predonation of blood before surgery has multiplied arithmetically. Also, the pathophysiology of anemia is being studied more extensively. Fortunately, the transmission of hepatitis through homologous transfusion may be decreased for a number of reasons, all because of our new transfusion practices. The National Institutes of Health have held consensus conferences involving the nations's experts and have formulated some contemporary guidelines for blood use. Therefore, although resulting in death for many of its sufferers, the AIDS crisis, by providing motivation to change medical practice, has had some major positive impact upon health care in the operating rooms.

Nevertheless, the AIDS crisis is not the only force behind the current revolution in transfusion practice. New surgical procedures, particularly liver transplantations, have required the transfusion of blood in quantities that previously were incomprehensible. As a result, new technologies for the administration of such massive quantities of blood have had to be developed. Coagulation monitoring technologies, some old and some of very recent development, applied initially in liver transplantation are now in use throughout all surgical fields. Clinical practices previously thought to be impossible, such as changing a patient's blood type intraoperatively, are now being carried out successfully.

In the future, because the US population is aging, both the number of surgical procedures and their complexity can be expected to increase. Relative blood loss during these procedures may increase as well.

Because today's technology is creating previously unimagined innovations, the future of blood transfusion is hard to predict. Work is proceeding on polyhemoglobin solutions, recombinant DNA-produced hemoglobin preparations, and lypholyzed coagulation plasma derivatives that may be virus-free. Research to uncover new, safe modes of treatment for the various hemorrhagic disorders encountered in the operating room is in the forefront of concerns confronting contemporary anesthesia practice.

To help anesthesiologists keep abreast of this rapidly changing technology, this issue presents information regarding the science, motivations, and clinical forces compelling the growth of operative blood transfusion medicine at the entrance to the 1990s.

I would like to acknowledge the secretarial, organizational, and editorial contributions of Ms. Phyllis Hood.

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FORTHCOMING ISSUES

December 1990

PREANESTHETIC ASSESSMENT
Elizabeth A. M. Frost, MD, *Guest Editor*

Proper anesthesia care must begin, by definition, with an appropriate preanesthetic assessment of the patient. If potential anesthesia problems are not recognized, anticipated, minimized, or eliminated, then the risk of perianesthetic complications is increased greatly. Thus, the cornerstone of good anesthesia care is proper preanesthetic assessment. This issue of *Anesthesiology Clinics of North America* will completely cover how to uncover all important preanesthetic problems. The guest editor, Dr. Elizabeth Frost, by virtue of her extensive clinical experience, personal writings, and previously published books, is a leading authority on this subject; the great intrinsic value of this issue is enhanced by her guest editorship.

March 1991

FIBEROPTICS IN ANESTHESIA
James T. Roberts, MD, *Guest Editor*

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June 1990

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December 1989

INFECTION IN ANESTHESIA
Arnold J. Berry, MD, *Guest Editor*

Anesthetic Care and Blood Loss

*Bruce D. Spiess, MD**

Unanticipated hemorrhage may occur during almost any surgical undertaking. Even procedures that seem minor (i.e., hemorrhoidectomy), under certain circumstances, can become major bloodloss events. However, these incidents occur very infrequently and, indeed, the need for large transfusion intraoperatively is rare. Each hospital or operating suite carries an indigenous mix of cases that has evolved over time based on surgical personnel, institutional strengths, and geographic locations. Practitioners in different institutions, therefore, hold individual frames of reference that shape their approaches to cases at risk for hemorrhage. Liver transplantation, multiple trauma, major vascular surgery, spine surgery, total hip replacement, hepatectomy, craniotomy, cardiopulmonary bypass, radical prostate surgery, craniofacial reconstruction, as well as many other procedures, may routinely require some transfusion of blood products. This article discusses several surgical procedures wherein hemorrhage has been studied and a few techniques to decrease blood loss.

The 1980s have seen a rapid growth in the number of liver transplant procedures performed. The number of cases has doubled through the middle and latter half of the decade.[34] Several thousand hepatic transplant procedures will be performed this year.[18] Orthotopic liver transplantation is no longer an experimental procedure. Since the 1960s when Dr. Starzel first pioneered the procedure, major blood loss has been an expected and sometimes devastating intraoperative event.[1, 2, 8, 10, 14, 17, 32] Hepatic transplantation has impacted on the blood banks and transfusion services of every hospital where it is performed. The impact of a liver transplant procedure requiring massive transfusion can affect bloodbanks at other hospitals or throughout an entire city. In some institutions it is the largest blood loss procedure routinely performed.

The reasons for abnormal hemorrhage are many. Patients with end-stage hepatic failure possess a complex coagulopathy characterized by a decreased concentration of circulating protein procoagulants, low fibrinogen concentration, depressed platelet counts, and enhanced fibrinolysis.[8] These defects, coupled with hemodynamic changes, fluid shifts, and blood loss, predispose these patients to further hemorrhage. The surgical procedure requires a deep dissection in the hepatic bed, which may be scarred from prior surgery or hepatitis. Portal hypertension may produce profound dilatation of splanchnic veins, which are often thin walled and exceptionally friable. The surgical challenge to control bleeding and accomplish a satisfactory dissection is tremendous.

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Data on blood utilization during liver transplantation is contained in Table 1.[8] This represents only one institution's experience. Patient selection, surgical skill, and the anesthesiologist's ability to treat ongoing coagulopathies influences the individual blood requirements of patients and institutions. Cases requiring as much as hundreds of units of blood have occurred, and there appears to be no way of predicting which case will require these incredible amounts of transfusion. The use of femoral/portal-vein-to-axillary-vein bypass may help decompress the splanchnic circulation during the anhepatic phase of the operation, although a direct connection between its use and a decrease in blood loss has not been proved.[31] The use of agents to decrease fibrinolysis during the anhepatic period does decrease hemorrhage at that time. Liver transplantations are new and challenging cases that require anesthesiologists to be particularly aware of the problems of transfusion medicine. Research and experience during these cases will not only benefit the future of hepatic transplantation but also the lives of patients undergoing many other procedures.

Multiple trauma victims can enter the operating room often without the full extent of their injuries being diagnosed, and they present major hemorrhagic risks. Like liver transplant cases, not all hospitals deal with major trauma cases. Hemorrhage from these cases may equal or exceed that seen during routine "controlled liver transplantation." Head trauma, aortic dissection, liver fracture, splenic rupture, and pelvic or hip fracture are some causes of severe blood loss. Often such injuries cause the immediate loss of circulating volume at the time of injury. Hypovolemic shock may be the cause of death prior to entry into a hospital emergency suite. Adequate resuscitation by emergency medical personnel may help to stabilize patients so they can reach an operating room; however, once surgical exposure is gained and tamponade of an injury site is removed, massive or uncontrolled hemorrhage may ensue. The experienced anesthesia team will anticipate such an event and adequate preparations will be made.

Two orthopedic procedures, total hip arthroplasty and major spine surgery, often require transfusion therapy and have been well studied.[7, 12, 20, 33, 35] Both procedures require extensive exposure of cortical bone. Osseous venous channels lack the ability to undergo constriction. That inability, combined with this vascularity, combine to create a situation wherein continuous slow oozing of blood occurs. As more surface area is exposed by surgical intervention, the amount and rate

Table 1. *Blood Utilization During Liver Transplantation*

PATIENT GROUP*	HOURS OF SURGERY	PREOPERATIVE THERAPY	WHOLE BLOOD UNITS	RED BLOOD CELL UNITS	FRESH FROZEN PLASMA UNITS	CELL SAVER UNITS	PLATELET UNITS	CRYSTALLOIDS MI
I	10.5	5 Yes	10.2	0	4.6	2.5	14	9460
	(8–15)	4 No	(7–16)		(1–10)	(0–30)	(0–30)	(6,400–12,500)
II	12.75	9 Yes	17.8	3.2	11.2	16.5	28	13,510
	(8.5–16.5)	4 No	(0–38)	(0–25)	(6–23)	(0–49)	(10–50)	(7,000–26,700)
III	13.0	8 Yes	17.5	4.5	9.2	21.2	26	13.480
	(10–19.5)	2 No	(0–40)	(0–17)	(2–18)	(5–48)	(10–47)	(5,300–25,000)

* Groups: I, normal hemostasis; II, coagulopathy during anhepatic phase; III, severe hemorrhage throughout the case.

From Dugdale M: Hemostasis during liver transplantation. *In* Williams J (ed): Hepatic Transplantation. Philadelphia, Saunders, 1990, p 231; with permission.

of total blood loss increases. Some changes in routine coagulation tests do show changes in coagulation function during total hip arthroplasty; however, these changes may not enhance bleeding until extreme blood loss is encountered.[7, 37] The activated partial thromboplastin time (APTT) is prolonged as surgery progresses; however, the prothrombin time (PT) appears to be unchanged.[7] Tissue plasminogen activator levels are unchanged; therefore, activation of the extrinsic pathway, monitored by the PT, is not enhanced. Levels of fibrinogen decrease throughout surgery and that may account for the prolongation of the APTT. Whole blood clotting function as measured by thromboelastography actually demonstrates a tendency toward mild hypercoagulation until extensive euvolemic hemodilution is required.[37] Coagulation changes therefore do not appear to contribute to or overcome the effects of surgical trauma during hip replacement. The anesthesia team should be aware that often patients undergoing total hip replacement will have been using aspirin or other arthritis anti-inflammatory agents. These agents affect platelet activation. Anesthetic techniques using epidural anesthesia, especially if continued-postoperatively, do affect coagulation postoperatively.[20, 22, 23] Patients using these techniques have a much quicker return to normal levels of antithrombin III and a lower incidence of postoperative thrombophlebitis and pulmonary embolism.

Blood loss during hip surgery has been reported to average from 500 mL to 1 L.[7] Certainly, surgical skill and patient pathology (i.e., reoperation) may change these numbers dramatically in any individual. Extensive research in anesthesia has investigated the use of regional (i.e., epidural or spinal) or general anesthesia for total hip arthroplasty. There is little doubt that the use of continuous epidural anesthesia and postoperative pain care decreases the incidence of pulmonary embolism. The reduction in blood loss intraoperatively with different anesthetic techniques appears to still hold some controversy. Some authors have shown dramatic decreases with epidural anesthesia, whereas others have shown no significant change in replacement requirement.[21, 30, 38]

Anesthetically controlled, deliberate hypotension has been used extensively during total hip arthroplasty and spine surgery.[3, 6, 9, 41] Since it was introduced into clinical practice in 1948, it has been applied to a wide range of surgical procedures and a great number of patients. Only in hip, spine, and cancer surgery has it been definitely shown to decrease blood loss, improve operating conditions, and decrease surgical time. In orthognathic surgery, Lessard et al[16] have shown a significant reduction in blood loss, whereas Fromme et al[11] have noted no reduction in blood loss with hypotensive anesthesia for this type of surgery. Although both Fromme and Lessard reported a significant incidence of transfusion, 62.5% versus 44%, the two studies cannot be exactly compared. The methods of producing hypotension were different. Patient positioning, surgical skill, and triggers for transfusion were also different. Lessard et al used a predominantly isoflurane-hypotensive anesthesia, whereas Fromme et al used nitroprusside as their major hypotensive agent. The surgical site of most hemorrhage is the osseous venous channels opened during osteotomies of the maxillary bone. Whether different hypotensive techniques affect blood loss from these bones is unknown.

Hypotensive anesthesia has been extensively studied. There is a reasonable debate in the literature as to which method or predominant agent is the safest. Deliberate hypotension controlled by sodium nitroprusside (SNP) infusion is physiologically considerably different than hypotension resulting from hemorrhagic shock, which is characterized by low cardiac output and high systemic vascular resistance. During hypotension induced with nitroprusside, the cardiac output tends to remain normal.[40] The afterload and, to some extent, preload is decreased, thereby decreasing relative circulating volume as the vaculature is dilated. Preload reduction in hypotensive nitroprusside infusion is much less than with blood-pressure-matched hypotension owing to hemorrhage. In one dog study, blood pressure, heart rate, central venous pressure, and pulmonary artery occlusion pressure were compared between SNP and nitroglycerin with no recognizable differences.[24] Cardiac output remained stable in that animal study with SNP infusion while systemic vascular resistance decreased slightly.[30]

SNP may provide a nearly balanced decrease in vascular resistance and venous capacitance. Nitroglycerin is thought to affect the venous circulation predominantly. Nitroglycerin in adult patients has been quite effective in reducing blood pressure and has been recommended as a method of producing deliberate hypotension. Sodium nitroprusside may be metabolized to cyanide; however, this is very rarely a problem during its acute utilization in the operating room.[5, 39] But that potential has led to the utilization of nitroglycerin. It does appear that cardiac output remains unchanged during nitroglycerin infusion. Conflicting reports of increased, decreased, or unchanged cardiac output with nitroprusside infusions in different surgeries are somewhat difficult to interpret. Heart rate definitely increases as a reflex with either infusion mediated by catecholamine release and activation of the renin angiotensin system.[4, 19, 29]

One study has compared both infusions in children. Very often, patients undergoing congenital spine deformity surgery and orthognathic surgery are children.[41] Nitroglycerin infusion was shown to be significantly less effective than SNP in lowering blood pressure to acceptable levels in these patients. Widespread use of beta-blocking agents were required to prevent reactive tachycardia in young patients receiving nitroglycerin. Patients using nitroglycerin could be maintained at 60 to 63 mm Hg mean arterial pressure, whereas those receiving nitroprusside ranged between 52 to 54 mm Hg mean arterial pressure.

The safe lower limit of deliberate hypotension is held to be 50 to 60 mm Hg. In normal human brain, autoregulation of blood flow is constant until the blood pressure falls below 50 mm Hg. In patients with histories of hypertension, the lower limit of autoregulation may be 70% of their normal mean arterial pressure.[15] Hypotension in the face of major arterial stenosis may produce end-organ ischemia. One dog study by Hickey et al[13] examined the effect of nitroprusside-induced hypotension on 2° of artificial coronary stenosis. Hypotension to 50 mm Hg created ischemia characterized by transmural electrocardiographic changes and myocardial lactate production. However, that ischemia was caused only in the most severely constricted arterial model with baseline coronary artery blood flow reduced to 40% of normal. The measured level of coronary perfusion pressure with combined severe stenosis and hypotension was only 12 mm Hg. Clinically, there is no way to know the true severity of any given coronary lesion, and therefore it does appear prudent to avoid hypotensive anesthesia in any patient with coronary disease.

Isoflurane has been advocated by some anesthesiologists as a method of choice for creating deliberate hypotension.[25, 28] Cerebral vascular surgery, particularly aneurysm clipping, is facilitated with hypotensive anesthesia. Cerebral blood flow is maintained or elevated during nitroprusside hypotension, whereas the cerebral metabolic rate is unchanged. Isoflurane can decrease cerebral metabolic rate ($CMRO_2$) and therefore decrease the oxygen demand of brain tissue.[26] Newman et al[27] found a 25% decrease in $CMRO_2$ in 12 patients undergoing craniotomy for cerebral aneurysm clipping with isoflurane hypotension using 2.3 ± 1.0% isoflurane. Isoelectric electroencephalograms may be produced with isoflurane concentrations of 2 MAC, which produces maximal $CMRO_2$ depression in animals. However, Newman's clinical study did not require 2 MAC to maintain the hypotension.

Calcium channel blockers, beta blockers, trimethaphan, captopril, and adenosine have all been used either alone or in conjunction with one of the compounds discussed previously. There is no perfect drug of choice for deliberate hypotension, but it is obvious that a number of regimens may be used to decrease blood loss. Preparation and advanced planning by the anesthesia team is necessary to provide a smooth and controlled deliberate hypotensive anesthetic.

Anticipation of abnormal blood loss during a particular surgical procedure will allow for advanced planning and preparation. Placement of adequate venous access is of paramount importance. Today, percutaneous placement of large-bore 8.5-gauge French catheters is routine for liver transplantation. Such catheters allow for the maximization of fluid flow in intravenous lines. Their usage in other massive hemorrhage cases such as multiple trauma is possible. Preparation of equipment for blood warming and, of course, securing adequate supplies of blood from the blood bank prior to embarking, appears to be simply common sense. Blood-warming systems are presently being introduced into clinical practice that maximize flow with efficient warming.

The growth of liver transplantation procedures has allowed for the development of an automated professionally manufactured rapid infusion system. Haemonetics Inc. (Braintree, MA) has produced a commercially available Rapid Infusion System (RIS) based on an original design from the University of Pittsburgh.[14] This technology allows for transfusions to be delivered at rates up to 1500 mL/min. An efficient heat exchanger will warm blood to 37°C even at such high-flow rates. Three built-in bubble detectors provide some safety from the deadly complication of massive air embolism should the reservoir run low. This technology is now used not only during liver transplantation, but for cases of multiple trauma, aortic aneurysm rupture, hepatic resection, and other cases of massive hemorrhage. Personal experience has shown this technology to be quite helpful during periods of blood loss that would have previously caused major hypotension. Much research is required to compare methods or recipes of priming the reservoir and the effects of altering the biochemistry of the blood transfused. Although the RIS machine sets up rapidly and can be attached to multiple intravenous lines, its use is most rewarding if anticipation and advanced planning are instituted.

This article cannot provide an exhaustive enumeration of cases at risk for hemorrhage. Clinical experience, especially within a particular institution and with different surgical teams, will provide the practitioner with an understanding of bleeding risk in his or her practice. Anesthetic techniques, particularly deliberate hypotension, may decrease bleeding, but anticipation is of the greatest importance.

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Tissue Oxygen Delivery

The Physiology of Anemia

*Kenneth J. Tuman, MD**

The process of oxygen delivery to tissues was well described six decades ago when it was noted that the basic requirements for adequate tissue oxygenation included a sufficient hemoglobin concentration, sufficient oxygenation of blood in the lungs, and a cardiac output sufficient to deliver an adequate supply of arterialized blood to the tissues.[4] In addition, the concepts developed by Krogh[59, 60] have remained the basis for understanding the transfer of oxygen from the microcirculation to the interior of tissue cells. Thus, while the basic principles regarding the transport of oxygen from ambient air to mitochondria have stood the test of time, many controversies remain regarding the definition of "sufficient" tissue oxygen delivery, as well as the optimum array of factors in the corporate process of oxygen transport (hemoglobin level, cardiac output, oxygen saturation, and so forth). The purpose of this article is to review the physiology of anemia, with special reference to tissue oxygen delivery, in the hope that this information will help clarify some of the controversial issues of tissue oxygen transport.

BASIC CONSIDERATIONS OF OXYGEN TRANSPORT

Transport of oxygen to body tissues is inarguably one of the most important physiologic functions of aerobic organisms. Tissue hypoxia will eventually result if oxygen delivery to tissues, the product of cardiac output and arterial oxygen content (Cao_2), is progressively lowered. Oxygen availability for the body as a whole usually exceeds resting oxygen requirements by two- to fourfold. In the anesthetized adult, for example, with a hemoglobin level of 15 g/dL, assuming Sao_2

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= 0.99, CaO_2 is approximately 20 mL/dL; with a cardiac index ranging from 2.8 to 4.0 L/min/m^2, delivery is between 560 and 800 mL/min/m^2. With a hemoglobin level of 10 g/dL and the same range for cardiac index, delivery varies between 380 and 540 mL/min/m^2. Total body oxygen uptake, on the other hand, is maintained near 105 to 115 mL/min/m^2 in anesthetized normothermic patients.[95] Therefore, a significant margin of safety for oxygen delivery as a whole exists, although there is a great variation in oxygen utilization between tissues. For example, organs such as kidney and skin extract only 5% to 10% of their total oxygen delivery (arteriovenous O_2 content difference/CaO_2), as compared with the heart, which extracts about 55% of its oxygen supply at rest.

The Fick equation defines that oxygen consumption (VO_2) is equal to the product of flow and the arteriovenous oxygen content difference (CaO_2 minus CvO_2). Thus, if the oxygen demand of a tissue such as myocardium increases, but the arteriovenous difference for that tissue cannot be increased significantly, the Fick relationship predicts that this increased demand (VO_2) must be met largely by an increase in myocardial blood flow.[107] In order to preserve the same total body oxygen uptake when anemia reduces arterial oxygen content, the Fick equation also predicts that either cardiac output must increase or that mixed venous oxygen content must decrease. If cardiac output does not increase, the increased extraction of oxygen from hemoglobin in the capillaries results in a decrease in the oxygen tension gradient to tissue. To maintain aerobic metabolism, a minimal oxygen tension gradient between capillary blood and intracellular mitochondria needs to be preserved. Thus, as the content of oxygen in the capillaries is reduced, a point is reached when there is not enough O_2 to supply cellular respiration, and O_2 consumption declines. The relationship between O_2 delivery (DO_2) and O_2 consumption (VO_2) is shown schematically in Figure 1. There is a biphasic character to this curve, with a region where VO_2 is essentially unchanged and not affected by wide changes in O_2 delivery, as well as a DO_2-dependent region. In the DO_2-independent region, decreases in O_2 delivery are compensated for by increases in the oxygen extraction ratio. Body tissues have a limit to their ability to increase the oxygen extraction so that, at some level of reduction in DO_2, full aerobic metabolism cannot be maintained and the VO_2 declines as a function of DO_2.

The level of O_2 delivery where the VO_2 becomes supply-dependent is known as the critical DO_2 ($DO_{2\text{-crit}}$).[10] Animal data show that when O_2 delivery falls below a critical value of approximately 10 mL O_2/min/kg,[10] VO_2 declines from an otherwise nearly constant 5 mL O_2/min/kg and VO_2 declines progressively with further reductions in O_2 delivery.[97] The biphasic relationship between DO_2 and VO_2 appears to occur regardless of the mechanism for declining DO_2.

With the exception of the data of Shibutani et al,[95] clinical studies have shown a linear relationship of oxygen delivery and consumption.[30, 31, 75, 82] The difference between animal experiments displaying a biphasic DO_2–VO_2 relationship and clinical studies showing a

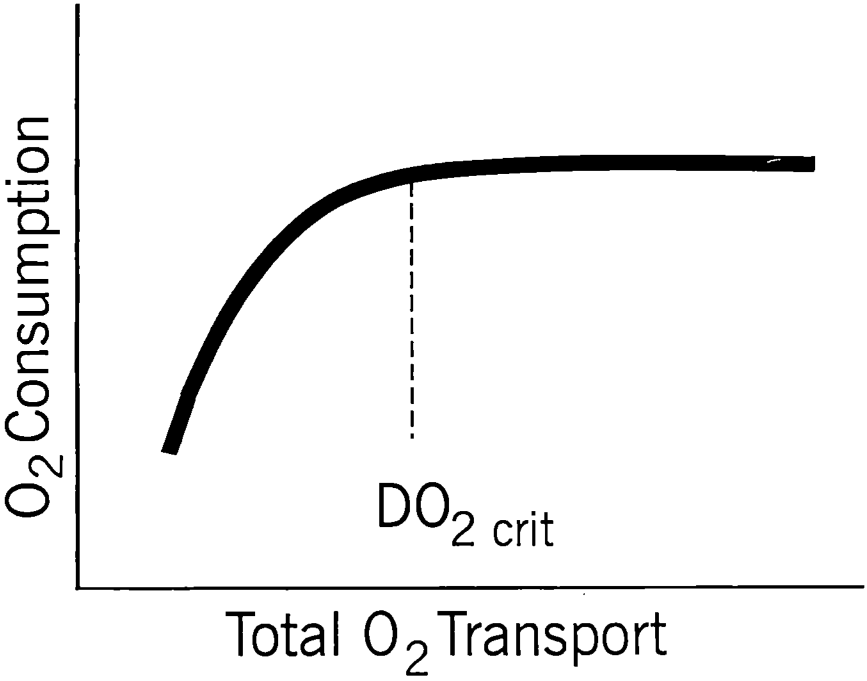

Figure 1. Schematic representation of the biphasic relationship of O_2 consumption to O_2 delivery determined from animal data. VO_2 remains constant until O_2 transport declines to a critical level (DO_2 crit), where it begins to decrease.

linear relationship may be explained by the increased basal Vo_2 in patients with acute lung injury [for example, adult respiratory distress syndrome (ARDS)] and sepsis, combined with decreased oxygen-extracting ability. Thus, unless supranormal levels of Do_2 can be achieved by the cardiopulmonary system, clinical studies may not be able to demonstrate the portion of the curve where Vo_2 is independent of Do_2, and the biphasic Do_2–Vo_2 curve is probably the true physiologic nature of the oxygen transport system.

Although $Do_{2\text{-crit}}$ is the same regardless of whether hypoxic, stagnant, or anemic hypoxia is used to reduce Do_2, the measured mixed venous partial pressure of oxygen varies significantly. When normovolemic reduction in hematocrit is used to limit Do_2, the Pvo_2 is about 40 to 45 mm Hg at $Do_{2\text{-crit}}$, whereas the critical Pvo_2 is about 17 to 20 mm Hg during hypoxic hypoxemia,[10] and about 31 to 36 mm Hg during stagnant hypoxemia.[51] There are several explanations for these differences in critical Pvo_2. One explanation is that Pvo_2 may not give a true representation of tissue oxygenation. It is commonly assumed that the Pvo_2 corresponds to the lowest O_2 tension along the length of the capillary.[101] The mathematical analysis proposed by Krogh to represent the tissue-capillary interaction has been combined with information about the capillary Po_2 profiles, but it still fails to

Table 1. *Maintenance of* DO_2 *During Normovolemic Anemia*

- Increased cardiac output
- Redistribution of cardiac output
- Capillary recruitment
- Alterations in capillary transit time
- Increased tissue oxygen extraction
- Changes in hemoglobin affinity

completely explain the discrepancies in PvO_2 measured at the critical DO_2 in various forms of tissue hypoxia. Regardless, the finding of a PvO_2 during normovolemic anemia that is much higher than when $DO_{2\text{-crit}}$ is achieved using stagnant or hypoxic hypoxia has been suggested to indicate that, in extreme anemia, there may be a limitation of O_2 uptake from the blood.

In the Krogh model of the microcirculation,[60] there are three mechanisms by which tissues can increase O_2 supply: recruitment of more capillary circulation, more blood flow through the existing capillary circulation, and more hemoglobin desaturation (Table 1). It has been suggested that the apparent limitation of oxygen extraction that occurs with anemia severe enough to produce $DO_{2\text{-crit}}$ may be related to the increased flow velocity and decreased transit time of the red cell through the capillary circulation.[45, 71] Although at moderate levels of hemodilution, the decrease in capillary transit time may be beneficial to tissue oxygenation,[72] at profound levels of anemia, the time available may be insufficient for diffusion of oxygen to tissue. Because some areas of the body are relatively overperfused, as compared with oxygen demand during anemic hypoxia, and because red blood cell (RBC) velocity greatly increases, peripheral shunting of blood may occur at the capillary level. Any functional shunting may produce an exaggerated effect on PvO_2 because of the flattening of the oxyhemoglobin dissociation curve for anemic blood.[11] Thus, distribution of blood flows to tissues of varying oxygen extraction, as well as the existence of functional shunts, may contribute to the disparity between mixed venous PO_2 for anemic hypoxia and stagnant or hypoxic hypoxia. Stated in other words, peripheral tissues may not extract all the oxygen presented to them, and in anemic hypoxia, peripheral regions that are relatively overperfused represent an incomplete compensatory adjustment to conserve oxygen stores.

Conversely, critical systemic oxygen transport, as well as fractional oxygen extraction, have been shown to be independent of hemoglobin concentration.[51] For a given VO_2, if systemic O_2 transport is the same at the critical point, whether cardiac output, hemoglobin, or SaO_2 are decreased, then the fractional O_2 extraction (CaO_2 minus CvO_2)/CaO_2 should be similar, regardless of the method of producing tissue hypoxia. Because (CaO_2 minus CvO_2)/CaO_2 may be approximated by (SaO_2 minus SvO_2)/SaO_2, one would predict that in stagnant or anemic hypoxia, as long as the SaO_2 was similar, the SvO_2 and, hence, Pv_{O_2} at the point of $Do_{2\text{-crit}}$ should be similar (unless mixed venous P_{50} or pH differ). Alternatively, the differences in critical Pv_{O_2} during anemic and hypoxic hypoxia may be explained if one assumes that the Sa_{O_2} is reduced during hypoxemia, so that the Sv_{O_2} and Pv_{O_2} must also be lower, as compared with that with low hemoglobin or cardiac output, given the assumption of a similar fractional O_2 extraction under all conditions of critical O_2 delivery.

CARDIOVASCULAR ADJUSTMENTS DURING ACUTE ANEMIA

As predicted by the Fick relationship, a rise in cardiac output commonly occurs during acute anemia (Table 2). The magnitude of the increase in cardiac output depends on the degree of hemodilution, and most of the increase is usually due to a rise in stroke volume, but this is dependent on the initial heart rate.[10, 16, 18, 32, 40, 68, 86] Although the increase in cardiac output is usually associated with increased stroke volume rather than increased heart rate, this holds true for normovolemic anemia only and clearly does not apply when anemia is associated with hypovolemia. It has been calculated that if blood had no hemoglobin in it, then a resting adult breathing room air would require a cardiac output of about 100 L/min to carry enough oxygen to the tissues to support basal metabolic demands.[24] Even if the heart were capable of performing such an immense job, it is extremely unlikely that the vasculature of the delivery-dependent tissues would be capable of containing such a flow. The cardiovascular response to anemic hypoxia with hematocrit less than 27% in dogs is associated with an actual increase in oxygen uptake until hematocrit declines to less than 10%,[13, 15] at which point V_{O_2} declines as O_2 delivery begins to fail. The mild increase in V_{O_2} has been attributed to increased myocardial oxygen uptake,[81, 105] as well as a metabolic action of catecholamines on muscle, which can be abolished by β-adrenergic blockade.[17]

The magnitude of the rise in cardiac output that accompanies acute normovolemic anemia is intimately related to a reduction in blood viscosity.[40, 79] Viscosity can be defined as a measure of "internal friction" in a laminar flow system.[21] The Poiseuille-Hagen Law de-

Table 2. *Mechanisms of Cardiac Output Increase During Anemia*

- Decreased blood viscosity
  - Decreased total peripheral resistance (afterload)
  - Increased postcapillary venular flow (preload)
  - Augmented venous return
- Increased sympathetic nervous activity
  - Augmented contractility
  - Increased venomotor tone (decreased capacitance)

scribes laminar flow ($\dot{Q}$) in noncollapsible tubes as follows: $\dot{Q} = \pi (P_1 - P_2)R^4/8\ nL$, where P_1 and P_2 = inlet and outlet pressures, respectively; R = tube radius; n = viscosity; and L = tube length. Thus, if the pressure drop and radius of a tube do not change from one end to the other, lowering blood viscosity will increase flow. Because blood is not a Newtonian fluid, its viscosity varies with conditions of flow. In very small blood vessels when flow is rapid, red blood cells line up with their discoidal surfaces facing each other and pass through in a column-like fashion.[37] Under such conditions, the effective viscosity is that of the plasma surrounding the column of RBCs. When blood flow diminishes below a critical rate, the axial streaming of RBCs does not occur and the cells become evenly distributed throughout the vessel, so that viscosity increases as hematocrit rises. The increase in viscosity with decreasing flow velocity is most marked at normal hematocrits, although the effect is attenuated at a hematocrit of 30%, and at a hematocrit of 15%, blood begins to lose some of its non-Newtonian characteristics.[22] Because anemic blood contains fewer RBCs, the three-dimensional rouleaux formation is less stable and can be broken up at lower shear rates.

Changes in viscosity of blood depend on flow rates and, therefore, also on blood vessel diameter. High shear rates and flow velocity occur in the aorta and major arteries, whereas low shear rates and blood flow velocity conditions occur in the postcapillary venules. For theroretical reasons, the postcapillary venules are likely to be the primary site of rheologic impact on flow.[93] Because of angioarchitectonic differences, the total cross-sectional area of the venules is larger than that of the arterioles; therefore, shear rates and stresses are lower than in the precapillary area. At low shear rates (11.5 sec^{-1}), such as those found in postcapillary venules, a reduction in hematocrit from 40% to 20% produces an eight-fold greater reduction in viscosity than at high shear rates (230 sec^{-1}), as may be found in the aorta.[65] Thus, the effect of reduced viscosity on blood flow is most noticeable in the postcapillary venules.[65] The profound reduction in viscosity seen in the postcapillary venule with moderate normovolemic anemia results in increased venous flow and may be the primary mechanism for the passive increase in venous return to the heart. This is supported by data from Murray and Escobar,[78] who demonstrated an increase in cardiac output when dogs were exchange-transfused with colloid to one half their normal hematocrit, but an actual decrease in cardiac output and $P\text{v}O_2$ in dogs whose effective hemoglobin was halved by exchange transfusion with RBCs containing methemoglobin. When the methemoglobin-treated dogs were further exchange-transfused with colloid to one half their normal hematocrit, cardiac output rose markedly, suggesting that viscosity changes play a significant role in the increase in cardiac output associated with normovolemic anemia.

It is important to note that the effects of inducing acute normovolemic anemia produce markedly different effects on whole blood, as compared with plasma viscosity. For example, dilution of blood with dextran progressively decreases whole blood viscosity, while the viscosity of plasma is significantly increased by the colloid concentration.[67] The increased plasma viscosity has been shown to actually improve the fluidity of blood by enhancing the deformation of RBCs and this effect is present at all shear rates.[67, 94]

Animal data have demonstrated that when hematocrit decreases from 40% to 20%, there is a slight increase in end-diastolic volume, minimal change in end-diastolic pressure and diastolic compliance, but a decreased end-systolic volume, thus explaining the increased stroke volume.[85] The decrease in end-systolic volume that occurs as hematocrit decreases occurs, in part, because the systolic function curve of the left ventricle shifts to the left, secondary to a reduced afterload.[40, 62, 79] The decrease in total peripheral resistance (R) is proportional to the decrease in blood viscosity (n) and the total vascular hindrance (Z): $R = nZ$.[20, 36] Part of the decrease in afterload that accompanies dilutional anemia has been postulated to occur as a result of peripheral vasodilation secondary to tissue hypoxia. Experiments using both normobaric and hyperbaric hyperoxia to abolish any possible tissue hypoxia during dilutional anemia have demonstrated little change in the cardiac output response, as compared with nonhyperoxic conditions.[32] The increased flow state that accompanies a reduction in blood viscosity has been shown to cause accentuation of the aortic component of the second heart sound, probably because of augmented diastolic vibrations of the closed valve associated with reduced clamping forces that act on the semilunar valve as it vibrates after closure.[98]

The decrease in vascular resistance not only decreases afterload, but also increases venous return.[40, 79] The increase in cardiac output that occurs with normovolemic anemia has been shown to be largely passive in nature,[46] because, during constant arterial and controlled right atrial pressures, venous return is inversely related to hematocrit. Wood[109] reported a decrease in venous distensibility in patients with anemia, and Chapler and Cain[14] observed a peripheral to central blood volume shift during the production of acute anemia, based on weight changes in canine hind limb. The translocation of blood attributable to these effects increases venous return and, therefore, cardiac output. Blockade of α-adrenergic receptors during anemia causes reduction in venomotor tone, peripheral pooling of blood, decreased venous return, and reduced cardiac output response.[15] Increased afferent activity from the aortic chemoreceptors has been documented during acute anemia,[48] and other studies suggest that the aortic chemoreceptors contribute to the increase in cardiac output during anemia by affecting the level of venomotor tone.[100]

To summarize, the effects of acute dilutional anemia on preload are largely mediated by reduction in the resistance to venous return. This reflects the marked effect of reduced viscosity in the setting of low shear rates on postcapillary venular blood flow. The degree of importance of this increase in venous return in contributing to a rise in cardiac output relative to the reduction in afterload by decreasing viscosity, as well as increased contractility, is currently unknown and no information exists at present to distinguish the specific contribution of each of these mechanisms. Data do exist, however, to demonstrate that sympathetic innervation of the heart is required to achieve the typical increase in cardiac output that occurs with acute anemia.[41, 49] Although cardiac sympathetic nerves help to maintain or augment the increase in contractility observed during acute anemia, direct β-adrenergic effects on the heart are not crucial for the cardiac output response to acute normovolemic anemia.[14, 19] A positive inotropic factor has also been described in the setting of chronic anemia.[39]

TISSUE OXYGEN DELIVERY DURING NORMOVOLEMIC ANEMIA

Although cardiac output increases as hematocrit is reduced, whole-body Do_2 reaches a peak value of about 110% of preanemic Do_2 when hematocrit reaches about 30% to 33%.[68] This occurs as a result of the exponential improvement in the rheologic properties of blood that occurs with linear decreases in hematocrit, particularly in the range of 45% to 30% where there is an optimal compromise between reduced O_2-carrying capacity and increased blood fluidity. Based on theoretical considerations, Hint[52] first predicted that systemic O_2 transport capacity increases with reduced hematocrit and reaches a peak value near a hematocrit of 30%. Duruble et al[34] more recently computed the relationship between systemic O_2 transport and reduction in hematocrit, and their results support the predictions of Hint, as well as the experimental data cited above. As hematocrit declines further, Do_2 declines, and at a hematocrit of about 25%, Do_2 falls below normoxic preanemic levels. Other workers[90] have also shown that total oxygen delivery increases as hematocrit is reduced toward 25% to 30%. Thus, more recent data refute earlier work suggesting that optimal oxygen transport occurs at a hematocrit level of 40%.[80] Richardson and Guyton[87] and Gump et al[44] used crystalloid hemodilution and suggested that the ideal hematocrit was 40%. These differences between studies may be related to the use of dextran versus crystalloid hemodilution, as well as other methodological differences in the exact hemodilutional procedures that produce different plasma viscosity changes at the same level of hemodilution. Thus, total oxygen transport varies minimally over a wide range of hematocrit between 25% and 45%, but above and below that range, O_2 delivery is decreased.

Tissue oxygen tension measured with multiwire oxygen microelectrodes[69] has been shown to increase in ischemic tissues to an extent that cannot be explained solely on the basis of the small increase in systemic oxygen-transport capacity (10%) that occurs with moderate degrees of anemia. With the increased flow velocity that occurs with isovolemic hemodilution, blood arrives in the capillaries with a greater amount of O_2, as compared with higher hematocrits with slower transit times, which allow greater time for O_2 to leak out of the vessel wall before reaching the exchange structures (i.e., capillaries).[61,72] It has also been established that mean blood pressure (BP) increases in arterioles and capillaries but remains unchanged in the postcapillary venules when hematocrit is lowered by normovolemic hemodilution.[73] This increased arteriovenous pressure gradient, in concert with improved blood fluidity, produces a more homogeneous distribution of tissue blood flow.[74, 104] Additional evidence to clarify the mechanism underlying improvement in tissue oxygenation by normovolemic anemia includes the recent finding that, in skeletal muscle, the local capillary hematocrit, which is about 30% to 80% of the systemic value,[57] remains nearly constant, unless the hematocrit declines to less than 15%.[63, 99] Other workers have also demonstrated an increase in the ratio of the microcirculatory to systemic hematocrit during normovolemic hemodilution, which may also contribute to improved oxygen delivery to tissues.[61, 64] These differences between microcirculatory and systemic hematocrit occur because of the complex interactions between axially migrating RBCs (Fahraeus effect) and the heterogeneous nature of the microcirculatory network.[103] Thus, a variety of mechanisms contribute to the increase in tissue oxygen delivery that accompanies mild normovolemic anemia and explain why the average O_2 tension in ischemic tissue shifts from 16 mm Hg at normal systemic hematocrit to 32 mm Hg when blood is diluted to 32% hematocrit.[66] These data suggest that normovolemic reduction in hematocrit may be significantly more effective in increasing tissue oxygenation under ischemic, as compared with nonischemic, conditions.[72]

REGIONAL BLOOD FLOW RESPONSES DURING NORMOVOLEMIC ANEMIA

Compensatory increases in cardiac output may require redistribution of blood flow to areas of high demand in order to effectively utilize the oxygen reserve held in venous blood during anemic conditions. Coronary and cerebral blood flow, for example, increase in association with regional vasodilation, such that flow to the heart and brain increase out of proportion to the rise in cardiac output seen with anemia.[5, 27, 105] This exceptional increase in blood flow to the heart and brain occur because these tissues are supply-dependent, while other circulatory beds, such as the splanchnic area, kidneys, and skin, are supply-independent. Supply-dependent tissues extract most of the consumable oxygen available, even under basal conditions, and cannot increase oxygen extraction further to avoid anaerobic metabolism. Maintenance of tissue oxygen delivery in supply-dependent tissues exposed to normovolemic anemia requires either recruitment of the capillary circulation or increased blood flow through those vessels already open.[59, 60]

The increase in myocardial blood flow is secondary to its increased demands; myocardial oxygen consumption more than doubles as hematocrit is reduced to 10% to 12%.[105] When this level of anemia is reached, coronary vasodilation is near maximal levels,[105] which allows total myocardial O_2 transport to remain near control levels until hematocrit levels decline below 10%.[36] When coronary blood flow can no longer match the increased energy demands of the cardiac pump, the increase in total body blood flow can no longer occur. This is consistent with the decline in whole body oxygen uptake that occurs at hematocrit values of approximately 10%.[13]

Normally, diastolic flow to the inner myocardium exceeds that to the epicardium, and it appears that the coronary vascular resistance is lower in the subendocardium than in the subepicardium.[58] The subendocardial vessels are closer to maximal dilation at rest than subepicardial vessels, and although the flow increase that accompanies acute mild normovolemic anemia initially maintains the endocardial:epicardial flow ratio, when hemodilution proceeds to a hematocrit of approximately 15%, this ratio may decline.[8, 9] This resultant "shunting" of blood away from the subendocardium may, under certain conditions, produce ischemic changes on the intracavitary electrocardiogram (ECG), even in animals with normal coronary arteries and normal aortic valves.[8, 9] More recent work using normovolemic hemodilution (hematocrit, approximately 20%) has demonstrated a transmurally uniform increase in left ventricular myocardial blood flow, in contrast to the relative subendocardial hypoperfusion demonstrated previously.[1, 25, 26] A possible explanation for this apparent discrepancy is that hematocrit was reduced to different levels in these contrasting studies, and that some tachycardia and aortic hypotension occurred in earlier studies and may have contributed to a reduced endocardial:epicardial flow ratio. Thus, subendocardial ECG evidence of ischemia has been shown to occur only if the hematocrit in animals declines below 15%; otherwise, no change in myocardial function or any signs of ischemia occur between a wide range of hematocrit from 40% to 20%. When hemodynamic variables are tightly controlled, selective hemodilution in the left anterior descending coronary artery causes equivalent increases in subendocardial and subepicardial blood flow.[25] During moderate degrees of normovolemic anemia (to a hematocrit of 20%), several lines of evidence suggest that oxygen demands of the left ventricular myocardium are satisfied. Coronary sinus blood Po_2 remains at baseline levels; monitored indices of global cardiac performance, such as left ventricular dP/dt, have been demonstrated to remain stable[28]; and continued uptake of lactate suggests the lack of anaerobic metabolism under these conditions.[81] Crystal and Salem[28] observed no change in regional oxygen consumption and myocardial segmental shortening with hematocrits as low as 10%.

In the presence of a moderate coronary artery stenosis, the improved blood rheology that accompanies a reduction in hematocrit to 17% is insufficient to increase flow distal to the stenosis to a degree great enough to offset the loss of oxygen-carrying capacity.[76] When left anterior descending coronary artery blood flow is reduced by a severe stenosis, regional myocardial dysfunction has been observed when hematocrit is reduced to 15%.[47] If critical coronary stenosis is present, hemodilution with perfluorocarbon attenuates the changes in regional dysfunction that occur with the same degree of hemodilution using dextran.[6] Clinicians are well aware that the presence of anemia may unmask the signs and symptoms of occult ischemic heart disease,[2] because myocardial oxygen demand may not be adequately met if coronary reserve capacity is depleted. The safe limits of hemodilution will thus depend on the severity of coronary lesions and the degree of impairment of coronary flow reserve capacity.

Cerebral blood flow also increases during anemia. When normovolemic anemia is induced to a hematocrit of about 10% in both experimental animals and humans, cerebral blood flow increases by up to 500% to 600% of control.[7, 54, 70, 84] This is, in large part, due to the decrease in viscosity, but at hematocrit levels less than 30%, increasing amounts of augmented perfusion are due to cerebral vasodilation so that cerebral blood flow increases out of proportion to the increase in cardiac output.[7] Lower hematocrits (20% versus 30%) have been associated with significant increases in cerebral blood flow during hypothermic nonpulsatile cardiopulmonary bypass with α-stat control of Pa_{CO_2}.[92] The lower cerebral blood flow at higher hematocrits during cardiopulmonary bypass are associated with a decrease in oxygen transport compensated for by an increase in oxygen extraction.[91] The increases in cerebral blood flow at lower levels of hematocrit may be the result of decreased viscosity, cerebral vasodilation, or abolition of hypocapnia-induced vasoconstrictor responses in the central nervous system observed under nonhemodiluted conditions.[29] Thus, normovolemic anemia may be of benefit in increasing cerebral blood flow and oxygen delivery under conditions of cerebral ischemia.[106] Hypervolemic anemia alone has also been shown to reduce the area of hypoperfusion during focal cerebral ischemia.[23]

The excess perfusion to the brain and heart during anemia occurs by a sparing of the limited oxygen supply to less vital tissues, which receive a less proportionate share in the rise in cardiac output. Studies have shown that relative vasoconstriction occurs in some tissues during acute anemia so that renal,[36, 43, 86] mesenteric,[36, 86] and hepatic[36, 86] blood flows are proportionately less than the total cardiac output response. The above-mentioned pattern of regional circulatory responses during normovolemic anemia remains intact in the presence of high-grade β-adrenergic blockade.[27]

Surprisingly, skeletal muscle blood flow during anemic hypoxia is not redirected to the extent that one might predict based on its large basal blood flow and oxygen uptake.[13] It has been postulated that the failure of skeletal muscle to redirect blood flow during severe anemia may be due to the greatly lowered blood viscosity with increased RBC flow velocity, which does not allow a given change in blood vessel diameter to be as effective in changing vascular hindrance to blood flow, as compared with conditions of normal viscosity. This postulate is supported by studies that demonstrate no effect of α-adrenergic blockade[15] or stimulation.[14] More recent work suggests that although

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humoral control (via the adrenergic system) may not be of paramount importance in regulating blood flow to limb skeletal muscle during dilutional anemia, experimental increases in sympathetic tone mediated by central neural pathways are able to influence hind limb vascular responses in this setting.[12] It remains unclear whether the stimulus of anemic hypoxia produces any significant increase in sympathetic tone to skeletal muscle or whether this increase is merely insufficient to overcome the countering effects of hypoviscosity on limb blood flow.

The compensatory cardiovascular changes during anemia vary not only with the degree of hemodilution, but also with time.[110] For example, a moderate degree of anemia (hematocrit equal to 30%) is acutely associated with major basal regulatory adjustments consisting of increased cardiac output and a low systemic vascular resistance, with maintenance of a normal PvO_2. Longer term adaptation consists of a return of systemic vascular resistance to normal and less of an increase in cardiac output, with redistribution of flow from organs with excess flow to those of greater need.[110]

The effects of hematocrit reduction on the coronary blood flow responses to exercise have also been studied. In animals undergoing submaximal treadmill exercise, global myocardial blood flow increases to 1.7 times basal levels at a hematocrit of 36%, and by 1.8 times basal levels at a hematocrit of 18%.[1] The distribution of blood flow to the left and right ventricles and interventricular septum, as well as the subendocardial:subepicardial blood flow ratio in these areas, does not change during exercise before or after this degree of anemia.[1] Submaximal exercise in the presence of normovolemic anemia does impair left ventricular function, as compared with the nonanemic state.[1, 89] Exercise produces greater increases in ventricular response (cardiac output) at a hematocrit of 20% than at control levels (39%) primarily because of increases in heart rate and contractility.[89] Despite the greater global hemodynamic adjustments that occur during submaximal exercise in the presence of anemia, the rise in blood lactate levels is greater than normal in the presence of anemia, suggesting that the hemodynamic compensation to meet the muscle-oxygen requirement is incomplete.[110] In addition, exercise at a 25% hematocrit reduction results in elevated norepinephrine, epinephrine, cortisol, and glucagon levels, increased hepatic glucose production and glucose metabolic clearance rate.[108] Exercise with anemia results in a more marked fall in plasma glucose than in normal exercising controls, but this is not the result of differential insulin responses.[42, 108] The increased dependence on blood glucose is a major metabolic adjustment to exercise under conditions of acute normovolemic anemia.

When tissue oxygen delivery falls below normoxic preanemic levels (i.e., at hematocrit less than 25%), oxygen extraction (CaO_2 minus CvO_2)/CaO_2 increases in order to meet tissue oxygen demands. In addition to increases in cardiac output and redistribution of blood flow to areas of high demand, other compensatory mechanisms occur. Multiple studies have demonstrated a shift of the oxygen dissociation curve to the right in patients as well as animals with different types of anemia.[3, 33, 35, 55, 77, 88, 102] The rightward shift in the oxygen dissociation curve is due to a rise in RBC 2,3-diphosphoglycerate (2,3-DPG) with a resultant fall in hemoglobin affinity for oxygen because of an increased proportion of deoxyhemoglobin. The increase in P_{50} that occurs with chronic anemia is enhanced during exercise because, with the increase in hemoglobin buffering for carbon dioxide, exercise brings about a greater than normal fall in venous pH, facilitating oxygen unloading at the tissue level (Bohr effect). Tissue oxygen tension in subcutaneous tissues has been measured in control and anemic animals and remains normal throughout a range of hematocrit from 20% to 40%.[50, 53] Collagen synthesis is supported and even slightly greater at lower hematocrit levels.[50]

The effects of acute normovolemic anemia on renal hemodynamics and plasma renin activity are complex. Hemodilution down to a hematocrit of 15% has been shown to result in a relatively constant renal blood flow.[56, 96] As noted previously, the resistance to blood flow (R) is determined by apparent blood viscosity (n) and vascular hindrance (Z), which represents the contribution of vascular geometry to flow resistance: $R = nZ$. With hemodilution, renal flow resistance remains relatively constant, while renal vascular hindrance increases as hematocrit falls below 20%.[96] This increase in vascular hindrance counteracts the decrease in apparent blood viscosity, resulting in relatively constant values of renal flow resistance. Plasma renin activity declines progressively with hemodilution to 25% hematocrit, but then increases markedly when the hematocrit falls below 20%, coincident with the increase in renal vascular hindrance. The large increase in renal vascular hindrance found at extreme levels of hemodilution may result from stimulation of plasma renin activity and subsequent elevation of angiotensin levels. Moderate normovolemic hemodilution causes renal vasoconstriction that may act as a stimulus for inhibition of renin release from the juxtaglomerular apparatus in the kidney. Marked normovolemic anemia may cause renal vasodilation because of local autoregulatory mechanisms to maintain tissue oxygen delivery, and this may act to stimulate renin release and subsequent production of angiotensin II. Erythropoietin production in the kidney is stimulated by declines in renal cell oxygen tension.[38] There is an exponential relationship between erythropoietin levels and linear reductions in hematocrit.[83] This increase in erythropoietin production is much more pronounced than that seen after reduction in renal blood flow (ischemic hypoxia), suggesting that the increase in renal production of erythropoietin due to anemia hypoxia may be triggered by one or more extrarenal signals.

SUMMARY

A variety of physiologic changes occur in response to the occurrence of normovolemic anemia. The majority of these changes reflect the body's attempt to maintain tissue oxygenation when total body oxygen delivery is compromised. These compensatory changes include an increase in cardiac output, redistribution of blood flow to tissues that are supply-dependent (i.e., heart and brain), and increased whole-body oxygen extraction. The increase in cardiac output is mediated by a variety of factors, including reduced blood viscosity, increased venomotor tone and venous return, and increased sympathetic nervous system activity. The aortic chemoreceptors increase sympathetic activity by responding to a decrease in blood oxygen concentration, as well as Po_2, which results in constriction of capacitance vessels and augmented venous return. To the extent that reduced viscosity contributes to increased blood fluidity and cardiac output, normovolemic anemia becomes self-correcting. Peripheral compensatory mechanisms that result in increased oxygen extraction allow more efficient use of a limited oxygen supply relation to tissues oxygen demands. These adjustments allow whole-body oxygen consumption to be maintained until the hematocrit falls to about 10%, at which point oxygen consumption becomes dependent on oxygen delivery. The decline in systemic O_2 consumption that occurs as hematocrit is lowered to about 10% corresponds to the exhaustion of coronary vasodilatory capacity, which limits further compensatory increases in blood flow. Although the complex pattern of physiologic responses to normovolemic anemia is largely understood, additional information is needed to elucidate the exact mechanisms of sympathetic vascular control of the peripheral circulation, as well as the responses of the microcirculation to normovolemic anemia. An appreciation of these complexities is important to the anesthesiologist managing the patient with a perturbation of oxygen delivery to tissues in the form of normovolemic anemia.

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Preoperative Hemoglobin Requirements

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For almost half a century clinicians believed that a hemoglobin level of at least 10 g/dL was necessary before subjecting a patient to anesthesia and surgery. The etiology of this requirement is cloaked in tradition, shrouded in obscurity, and unsubstantiated by clinical or experimental evidence. Yet, until recent years, it remained a standard of anesthetic practice.

THE EARLY YEARS

The very early anesthetic and surgical literature makes no reference to acute or chronic anemia. However, prior to the turn of the century, approximately five decades after the introduction of general anesthesia, a hemoglobin level below 30% of normal was considered unsafe because it left no margin for error. Patients tended to develop pulmonary edema at levels below 20%, and death during surgery was thought to invariably occur at hemoglobin levels of 15% or less.[11] In the late 1890s, anesthetists and surgeons turned their attention to the effects of anesthetics on the formed elements and hemoglobin content of blood. Anesthetics were thought to retard the movement of oxygen in the blood, and reducing agents were said to deprive hemoglobin of its oxygen with great difficulty. It was recognized that more anesthetic agent was present in the red blood cell (RBC) than was contained in the "fluid portions of the blood," and it was believed that quantities of blood corpuscles were destroyed by the anesthetic agent. A fall in hemoglobin was reported along with an alteration in the shape of the RBC.[21] This was said to be most marked in the presence of anemia. Prolonged anesthesia was held to "profoundly deteriorate the

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blood and militate against recovery," making rapid surgery most desirable.[11] Fish,[12] in 1899, offered evidence to support the reduction of hemoglobin levels and red blood corpuscle destruction by ether. More importantly, he expressed the belief, albeit based on false premises, that in patients with less than 50% hemoglobin, "oxygen is taken away from red corpuscles which are so poor in that element that they cannot spare it." As a result, he held that the red corpuscles were unable to give up oxygen to the tissues and such patients, when subjected to"etherization," would show evidence of "collapse." He further opined that the safest rule was not to administer an anesthetic if the hemoglobin was under 50%. An amount of anesthetic that was perfectly harmless when there was 80% hemoglobin could, according to Fish, be extremely dangerous when there was but 50%.

An elegant, for its time, clinical investigation by Da Costa and Kalteyer[11] put to rest the concept of RBC destruction by anesthetics. Their report is most important, however, for it is the first to recommend routine preoperative hemoglobin determinations. While they considered a "very low percentage" of hemoglobin to be a contraindication to the administration of general anesthesia, the amount that should be regarded as an absolute contraindication was uncertain. Although a level below 50% was considered dangerous, several patients survived surgery with hemoglobin levels of 40% or less. This led to the general recommendation, "If there is a low percentage of hemoglobin local anesthesia should be employed whenever possible."[11]

No further mention is made of a hemoglobin requirement for the surgical patient from the turn of the century to the Great War. At that time, controversy revolved about the safest anesthetic agent for the anemic patient. The prevailing opinion was summarized by Gwathmey[18] when he wrote, "Weak, anemic men and middle aged women yield better to nitrous oxide with oxygen either alone or supplemented by small amounts of ether or chloroform." Chloroform, ether, or ethyl chloride as the primary agents were thought to be contraindicated. Between the World Wars, anesthetists, sensitized by the classic work of Barcroft, held that a minimum hemoglobin level was one that would allow for the detection of cyanosis. A level of 8 g/dL was considered safe, predicated on the appearance of cyanosis in the presence of 5 g/dL of reduced hemoglobin.

THE MAGIC 10 GRAMS

The first available reference in surgical or anesthesia literature to the 10-g requirement appeared in 1941. Adams and Lundy[1] of the Mayo Clinic wrote concerning anemia discovered during the preoperative evaluation of the surgical patient:

> This condition, owing to the lowered oxygen carrying capacity of the blood, interferes with adequate transportation of oxygen to the tissues. When the concentration of hemoglobin is less than 8 to

> 10 grams per 100 cubic centimeters of whole blood, it is wise to give a blood transfusion before operation.

This recommendation, later abbreviated to 10 g, appeared in virtually every textbook on anesthesia written in the English language between 1941 and the 1980s.

In 1947, an influential group of surgeons lead by Clark et al[6] proposed a syndrome in patients designated "chronic shock." They postulated, and indeed presented some experimental evidence for, a deficiency in plasma proteins and hemoglobin in chronically ill patients. Their results led them to conclude

> because the time required for red blood cell and hemoglobin synthesis may fail to meet the surgical exigency in this population and because wound healing is slowed and convalescence greatly retarded, transfusion to normal values is recommended.

This dictum was passed on to surgeons who read the following in a standard text[7]: "It may be generally stated that no patient with a hemoglobin level below 10gm/100ml should be operated upon without correction of the anemia."

Scientific credence was provided in 1964 by Nunn and Freeman,[25] who presented a theoretical concept of oxygen flux. Their thesis depended on the amount of oxygen available to the body in unit time, i.e., the rate at which oxygen is made available to the tissues and equals the product of cardiac output and arterial oxygen content. Two factors determine the arterial oxygen content: hemoglobin concentration and arterial oxygen saturation. In normal resting humans, the available oxygen is calculated as 1000 mL/min while oxygen consumption or demand has been calculated at 250 mL/min. Utilization, then, is but 25% of supply. While the authors admit that it is difficult to define the lower limit of available oxygen compatible with survival, they tentatively suggest that 400 mL/min is the lowest rate that should be tolerated for even a short period during anesthesia. This theoretical discussion, however, did not consider compensatory mechanisms brought into play during chronic anemia or iosvolemic hemodilution. These authors did, however, recognize that

> a considerable amount of surgery in the world is carried out with hemoglobin concentrations of less than 8g/100ml. Provided the cardiac output and saturation are well maintained, the patient usually survives. The situation is, however, critical and no mishap must mar the administration of the anesthetic.

Once again, no mention is made of the potential for increases in cardiac output, changes in the oxygen-hemoglobin dissociation curve, or the oxygen content of the blood.

Anesthesiologists and surgeons were not alone in promulgating the 10-g concept. Hematologists must assume some degree of responsibility. In 1967, Mollison[22] wrote

> There is evidence that when the packed cell volume falls below about 30 percent corresponding to a haemoglobin concentration

> of about 10g/100ml, there is some interference with cardiac function. Therefore, before surgery is undertaken the haemoglobin should be raised to this level even if only trivial hemorrhage is expected. Before major surgery it seems desirable to raise the haemoglobin level to within the normal range; that is to say above 12.5g/100ml in women or 13.5g/100 ml in men.

The recommendation was based on something of a misinterpretation of the work of Case et al,[5] who studied the effects of acute isovolemic hemodilution on cardiac function in dogs ventilated with air. They reported depression of the ventricular function curve at a hematocrit of 24% (Hgb 8 g/dL). This value is significantly below that recommended by Mollison and others. It is indeed unfortunate that Mollison[23] quotes the same work as late as 1983 and only in the past 2 years has he gone on record as recommending medical rather than transfusion therapy whenever possible.[24]

As a result of this dictum promulgated by distinguished anesthesiologists, surgeons, and internists, a generation of anesthesiology program directors inculcated their residents with this minimal hemoglobin requirement. When challenged by a thinking resident they invoked the "Requirements for Accreditation of Hospitals," published by the Joint Commission on Accreditation of Hospitals. The Commissioners, however, must be held blameless. An exhaustive review of their documents reveals that their only requirement was the performance of a urine analysis and a hemoglobin or hematocrit determination on every patient admitted to a hospital. The same may be said of the Commissioners' forebears, the Regents of the American College of Surgeons.

ISOVOLEMIC ANEMIA

The rigid requirement for 10 g of hemoglobin prior to surgery began to unravel in 1958 when Crosby[10] likened routine use of blood to the secretarial practice of medicine. In such a practice a stenographer types a laboratory request and when the patient "fails" the hemoglobin test, she prepares a transfusion requisition. Experience during the Korean conflict demonstrated that as long as blood volume was maintained, the vital signs did not begin to show deficiency of oxygen-carrying capacity until the hemoglobin concentration was less than 7 g/dL. Comparing his military experience to civilian practice, Crosby observed, "Thoughtless prescription of blood transfusion is playing Russian roulette with bottles of blood instead of a revolver. While the odds are in the physician's favor that nothing will go wrong, the patient takes the risk." The following year, Shields and Rambach,[32] reviewing blood transfusion in surgical practice, commented, "It may be generally stated that no patient with a hemoglobin level below 10gm/100ml should be operated upon without correction of the anemia." However, they go on to observe that an evaluation of the inherent risks of transfusion versus the risks inherent in delaying surgery is logically required. This, then, is the first real plea for individual consideration.

In 1960, Renden and his associates[28] published their classic work comparing plasma volumes and RBC mass in a series of normal, cachectic cancerous, and noncancerous patients. They not only offered conclusive evidence against the concept of "chronic shock" advanced by Clark[6] two decades earlier, but demonstrated the danger of volume overload when the chronically ill are transfused. They pointed out that in the presence of chronic anemia, the plasma volume was most often increased, frequently to supranormal values. In the absence of acute blood loss, blood transfusion should not be given to correct deficits in blood volume that have not been demonstrated by accurate measurements. To do so, in the opinion of these investigators, "is often nothing more than pernicious meddling."

CONTEMPORARY STUDIES

Further indication that 10 g of hemoglobin was not an absolute requisite for major surgery came in the early 1960s when Cooley et al[8] introduced crystalloid as the volume prime for the pump oxygenator. This group and others[3, 9, 13] successfully managed patients with hematocrits of 20% or lower during cardiopulmonary bypass. This practice is now almost universal, for there is evidence that perfusion of many organs is actually improved by the lowered hematocrit.[29] Indeed, in at least one series, transfusion in the postoperative period was not thought to be indicated until the hematocrit fell to 22% or the patient became symptomatic.[9] The recognition that anemia, per se, does not equate with hypovolemia became even more obvious as anesthesiologists became more conversant with the management of patients with chronic renal failure.[2, 14, 17, 30, 33, 36, 37] These patients frequently presented for surgery with hemoglobin levels in the range of 5 to 7 g/dL, were normovolemic or hypervolemic, and if anesthetized with care recovered with no untoward effect.

Two retrospective studies published in 1970[20, 27] indicated that there was an apparent increase in morbidity and mortality in the anemic patient during surgery or in the early postoperative period. The increase, however, was not significant, and it was thought that the reduced hemoglobin level represented the underlying disease that necessitated surgery. A decade later, Carson et al[4] reported that operative mortality was inversely related to the preoperative hemoglobin level in a group of 125 anemic patients with a mean hematocrit level of 7.6 g/dL. Although the researchers concluded that the hemoglobin level is an important independent predictor of postoperative death, they did question the transfusion threshold of 10 g/dL, because no patient whose hemoglobin was between 8 and 10 g/dL died unless the blood loss, during surgery, exceeded 500 mL.

A recent 1-year prospective study[35] of patients with hemoglobin values less than 10 g/dL was undertaken in a tertiary care university medical center. Three hundred forty patients received 473 anesthetics. Anemia did not appear to increase morbidity or mortality in this group of patients whose mean hemoglobin was 8.6 g/dL. In another study,[16] the mortality rate in a series of eight patients with a mean hemoglobin level of 3 g/dL who refused transfusion for religious reasons but who did receive Fluosol-DA was 87%. From the available data it is reasonable to conclude that a hemoglobin level of 10 g/dL is not necessary in the normovolemic patient and that a value of 3 g/dL is associated with significant mortality.

THE NEW ERA

Although these studies provided incontrovertible evidence that demonstrated the safety of anesthetizing those patients who had less than 10 g/dL of hemoglobin, anesthesiologists were reluctant to change their ways.[19, 37] The adverse effects of transfusion, including the transmission of infectious agents by homologous blood, were well recognized. It was only the recognition of transmission of the retroviruses that changed long ingrained practice habits. Most anesthesiologists,[36] some reluctantly, now recognize that the majority of normovolemic patients who have less than 10 g/dL of hemoglobin can be safely anesthetized.

If 10 g/dL is not the absolute minimum and 3 g/dL is associated with significant mortality, what is the lowest acceptable hemoglobin level? Can an arbitrary value be established that is applicable to all or at least to most patients? Reported experience regarding anesthesia and surgery in an otherwise healthy anemic patient is, at best, sparse. What is known results to a great extent from the work of Gould et al.[15] These investigators have demonstrated rather conclusively in primates, and to a limited extent in humans,[16] that the hemoglobin level should not be the sole criterion for determining when RBC transfusion is required. While hemoglobin is the most significant, it is not the only determinant of oxygen transport. They showed, as did Nunn and Freeman[25] a decade earlier, that there is a significant reserve in the oxygen delivery and utilization system. Oxygen delivery represents the product of blood flow or cardiac output (CO) and arterial oxygen content.

$$O_2 \text{ delivery} = \text{CO} \times [O_2]_a$$

where $[O_2]_a = 1.34 \times \text{Hgb (g/dL)} \times \%O_2 \text{ saturation} \times 0.003 \times Pa_{O_2}$. A fall in hemoglobin, and thus of oxygen content, will result in a fall in O_2 delivery unless there is a concomitant increase in CO. In anemic patients with good cardiac function, such an increase does occur. Adequate tissue oxygenation thus can be maintained at hematocrits as low as 20% to 25%. An additional compensatory mechanism in the chronically anemic patient is the increase in 2,3 diphosphoglycerate. The resultant shift in the oxygen-hemoglobin dissociation curve may produce only a 27% decrease in oxygen availability with a 50% decrease in hemoglobin.[30]

The adequacy of the oxygen supply at any given hemoglobin level for any given patient becomes the paramount issue. The utilization of oxygen by the tissues can be calculated as the product of CO and the difference between arterial and venous oxygen content.

$$O_2 \text{ consumption} = CO \times ([O_2]_a - [O_2]_{\bar{v}})$$

Thus, the mixed venous oxygen content becomes the key to assessing oxygen transport and the need for transfusion. Another physiologic indicator, the extraction ratio (ER),[39] has been used. The ER represents the ratio of oxygen consumption to delivery.

$$ER = \frac{CO \times ([O_2]_a - [O_2]_{\bar{v}})}{CO \times [O_2]_a}$$

$$ER = \frac{[O_2]_a - [O_2]_{\bar{v}}}{[O_2]_a}$$

Because the normal $[O_2]_a$ is 20 vol% and the normal A-V_{DO_2} is 5 vol%, the normal ER is equal to 25%. Thus, as pointed out by Nunn and Freeman,[25] there is a reserve of 75%. In extreme normovolemic anemia when the ER is greater than 50%, myocardial lactate production is noted to occur. In the experimental animal, a decrease in mixed venous oxygen content and an ER in excess of 50% in not seen until the hematocrit falls below 10%. Available data from 15 patients indicate that a mean hemoglobin of 7 g/dL was tolerated, and the patients did as well as others who would usually be transfused at a similar level of anemia. While further validation is required, the ER together with the patient's condition may be an appropriate "transfusion trigger."

Shoemaker et al[33] have provided additional evidence that oxygen debt, calculated from oxygen delivery and oxygen consumption, is a determinant of lethal and nonlethal postoperative organ failure.

It is evident from these studies that all aspects of oxygen delivery and utilization, not just the hemoglobin concentration, must be taken into account in determining the need for RBC transfusion. Considering all of the factors that determine oxygen utilization, why the emphasis on hemoglobin? The answer is simple: hemoglobin is easy to measure while the other determinants were, until recently, relatively difficult to obtain. The advent of extensive invasive and noninvasive monitoring has made it possible to measure all of the factors that contribute to oxygen delivery and consumption.

The 1988 National Institutes of Health Consensus Conference on Perioperative Red Cell Transfusion,[27] considering this and other available data, came to the following conclusion:

> The decision to transfuse a specific patient should take into account the duration of the anemia, the intravascular volume, the extent of the operation, the probability of massive blood loss, and

> the presence of coexisting factors such as impaired pulmonary function, inadequate cardiac output, myocardial ischemia, or cerebrovascular or peripheral circulatory disease. These factors are representative of the universe of considerations that comprise clinical judgement.
>
> No single measure can replace good clinical judgement as the basis for decisions regarding perioperative transfusion. However, current experience would suggest that otherwise healthy patients with hemoglobin values of 10g/dL or greater rarely require perioperative transfusion, whereas those with acute anemia with resulting hemoglobin values of less than 7g/dL will frequently require red cell transfusions. It appears that some patients with chronic anemia such as those with chronic renal failure tolerate hemoglobin values of less than 7g/dL. The decision to transfuse will depend upon clinical assessment aided by laboratory data such as arterial oxygenation, mixed venous oxygen tension, cardiac output, the oxygen extraction ratio and blood volume, when indicated.
>
> It is essential to recognize that the combination of hypovolemia and anemia may lead to severe morbidity and/or mortality and that there is a minimum hemoglobin value for each individual below which severe morbidity and/or mortality due to inadequate oxygen delivery is likely to occur.

Except for the critically ill, values obtained from invasive and noninvasive monitoring devices are usually not available. The decision to transfuse or not must be made on the basis of clinical judgement alone. While isovolemic anemia may be well tolerated, it may not be the optimal state. This consideration must be balanced against the hazards of transfusion. There is danger that the suggestions of the Consensus Conference will be misinterpreted and that 7 g/dL will become the new "magic number" or transfusion trigger. There can be no magic number. It is just as dangerous to withhold an indicated RBC transfusion as it is to administer such a transfusion that is not indicated.

SUMMARY

The current state of preoperative hemoglobin requirements was best summarized by Graves and Allen:[17]

> The time honored limit of 10 grams of hemoglobin seems to be based more on theory than on clinical or experimental evidence. This limit is predicated on the assumption that because there are times during anesthesia when tissue oxygenation is dangerously critical, especially if the anesthetic technique is flawed, one should, therefore, transfuse to increase the patient's margin of safety.

Recent clinical experience, along with modern monitoring modalities and contemporary anesthetic agents and techniques, make any rigid requirement unnecessary. Blood is not a tonic nor does it hasten wound healing. Anemia per se is not an indication for transfusion. The necessity to increase the oxygen-carrying capacity of the blood is the only indication for transfusion of red blood cells. The transfusion trigger is variable and must be decided on the basis of clinical judgement aided by laboratory determinations when these are available. There can be no magic number.

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Coagulation Function in the Operating Room

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Hemorrhage in the operating room may be independent of coagulation defects; however, it may also be related to coagulopathies. A comprehensive understanding of coagulation function is of great value to the contemporary anesthesiologist. Bleeding and coagulopathies are expected and should be planned for in the operating room. The dynamic status of the coagulation system will affect the extent of hemorrhage. Today, blood product use must be adequately justified and documented. The use of coagulation products for "clinical indications" can no longer be supported and may be dangerous. All blood products carry the risk of transmission of infectious disease and other potential complications; furthermore, zealous component therapy may contribute to dangerous hypercoagulable states.[69] This article reviews coagulation function, enumerates cases that are at risk for preoperative or intraoperative coagulopathies, discusses routine monitoring techniques, examines some new monitoring technologies, and elaborates on contemporary coagulation therapy.

COAGULATION MECHANISMS: A REVIEW

The coagulation mechanism may appear to many clinicians to be too complex to master. Unfortunately, that impression has led to widespread disregard and underinvestigation of coagulation problems in the operating room. Hemostasis is a dynamic process. Successful arrest of hemorrhage is dependent on four interrelated mechanisms functioning together: the vasculature, platelet activity, protein cascade, and fibrinolytic system. Interactions with the complement system, bradykinins, kinins, and protease inhibitors augment and extend the

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physiologic affects of coagulation beyond the four above-mentioned areas of the system.

Vasculature

Macrovascular integrity is a fundamental necessity for adequate hemostasis. Surgical control must be gained on large vessels before coagulation can take place. The microvasculature is a strong regulator of the coagulation process. When ruptured, the microvasculature undergoes local reflex vasoconstriction, diversion of blood flow by dilatation of adjacent arterioles, and activation of platelets and the intrinsic and extrinsic coagulation cascades.[44]

The relative importance of vessel activity depends on vessel size. Capillaries may seal spontaneously, whereas arterioles and venules are sealed by platelet plug formation. Hemostasis of veins requires either surgical control or vascular contraction before other coagulation processes can contribute.

Normally, blood is prevented from coagulating by the action of the vascular endothelium. A mucopolysaccharide, glycocalyx, is produced by endothelial cells and excreted to coat the entire inner surface of the vasculature.[52] That mucopolysaccharide creates a nonwettable surface that prevents the interaction of platelets and coagulation proteins with collagen. Heparin sulfate is excreted as part of that complex.[5]

The vascular endothelium produces adenosine diphosphatase (ADPase).[51] Adenosine diphosphate (ADP) is a strong stimulant of platelet adhesion; therefore, the action of ADPase decreases platelet adhesion. The endothelial cells also produce prostacyclin (PGI_2), a potent vasodilator and platelet inhibitor. Prostacyclin is produced from arachidonic acid by cyclo-oxygenase in the same way as thromboxane is produced in platelets.[28] This enzyme system is susceptible to aspirin poisoning in the same way as the cyclo-oxygenanse system in platelets.[68] However, larger doses are required to affect the endothelial cells than those required to block platelet function.

The endothelial cell membranes contain receptor sites for the products of coagulation. Thrombin binds to these receptor sites (thrombomodulin), which, in turn, triggers the release of an anticoagulant known as protein C. Protein C activates plasminogen, furthering fibrinolysis, thereby helping to maintain a patent vasculature.

If the endothelial integrity is broken, collagen present in the basement membrane becomes exposed. That exposure is a strong stimulant for coagulation. Understanding coagulation dynamics begins with the actions of the vascular endothelium.

Platelets

After adequate vasoconstriction has occurred, platelet interactions provide the first line of defense against hemorrhage. Therefore, they form the foundation of primary hemostasis. Platelets are produced in the bone marrow by megakaryocytes and have a wide range of functioning subcellular organelles. Platelets act as metabolically active cells, producing proteins and other chemomessenger compounds, and undergoing cellular metabolism. However, they do lack a cell nucleus and therefore cannot replicate.

Platelets average 2.4 μm and have a normal circulating life of 9 to 12 days. A normal platelet count is 150,000 to 300,000 mL, although stress, infection, and transfusion of platelet-rich blood products may acutely elevate that level.[70] Thirty percent of platelets are harbored in the spleen and may be released into circulation if stressful stimuli are encountered. Lowered platelet counts may be caused by sepsis, chronic disease, bone marrow suppression, diffuse intravascular coagulation, and drug suppression of platelet production. Patients with pathologic splenomegaly caused by a number of etiologies might have a lower platelet count and a shorter platelet circulating half-life.

The importance of platelet function cannot be stressed too greatly. Adequate function is dependent on the action of the platelet membrane and the intracellular organelles. The membrane is unique in that it provides (1) for the physical interaction with the vascular endothelial surfaces and is the frontier for interaction with other platelets; (2) for sites of activation of the platelet; (3) for interaction with the protein coagulation cascade (factors V and VIII are embedded in the platelet membrane).[13, 43] Multiple coagulation cofactors require phospholipid as coenzymes before they act as proteases and the platelet surface supplies that requirement.[25]

Platelets' intracellular organelles are composed of mitochondria, endoplasmic reticulum dense granules, nonspecific granules, liposomes, and microtubules, as well as others. The microtubules function as a cellular cytoskeleton that is actively contractile, utilizing ATP for actin-myosin interaction. When stimulated, the platelet actively changes shape from a flexible discoid to a spiculated sphere that enhances its adhesive qualities and greatly increases its cell surface area.

Multiple stimuli may activate platelets in a graded manner. ADP, collagen, epinephrine, thrombin, ristocetin, arachidonic acid, complement immune complexes, and some medications may each bind to the platelet membrane, triggering its activation.[8, 51, 52] The initial platelet reaction is a morphologic change in shape. As more stimulation and/or more potent stimulation occurs, the cell membrane becomes sticky and primary aggregation occurs. Primary stimulation is reversible. It does require energy, but it does not consume platelets or permanently affect their function. Secondary aggregation occurs with stronger stimuli and is marked by prostaglandin synthesis and granular release. Alpha- and dense-granules are released, and eventually, lysosomes are exocytosed.

Prostaglandin metabolism is of major importance to the normal functioning of platelets. Phospholipids may be enzymatically reacted (with platelet cyclo-oxygenase) into a number of prostaglandins. Platelet cyclo-oxygenase is affected by a large number of compounds including the salicylates and nonsteroidal antiinflammatory agents. However, a number of other compounds, including β-blockers, calcium channel blockers, and some antibiotics (Table 1), decrease plate-

Table 1. *Medications Decreasing Platelet Activity*

- Thrombocytopenia
  - Acetaminophen
  - Cephalothin
  - Gentamycin
  - Sulfanamides

  - Acetazolamide
  - Chlorothiazide
  - Ethacrynic acid
  - Furosemide
  - Heparin
  - Protamine
  - Quinidine

- Unknown mechanisms
  - β blockers
  - Calcium channel blockers
  - Antihistamines
  - Antibiotics
  - Phenothiazines
  - Tricylic antidepressants
  - Nitroglycerin
  - Nitroprusside
  - Hydralazine

- Cyclo-oxygenase inhibition
  - Aspirin
  - Indomethacin
  - Ibuprofen
  - Naproxen
  - Sulfinpyrazone
- Increased cyclic AMP
  - Isoproterenol
  - Adenosine
  - Iloprost
  - PGI_2, PGE, PGD
  - Aminophylline
  - Caffeine
  - Theophylline

let function through a number of mechanisms.[33, 38, 45, 47] Low dosages of salicylates will not affect the production of PGI_2 by the endothelial cells.[47] Salicylate therapy will decrease platelet activity within 2 hours of ingestion and will inhibit the function of platelet cyclo-oxygenase in developing platelets for the life of the platelet. It will not poison already active platelets. Clinical practice has dictated that medications depressing platelet function are discontinued at least 1 week prior to elective surgery if normal platelet activity is to be assured.

Protein Cascade: Formation of Fibrin

Platelets are responsible for primary hemostasis, and the fibrin-forming coagulation cascade is responsible for secondary hemostasis. Of course, this is probably too simplified an explanation, because both activities occur at the same time and interaction between platelets and fibrin trigger each other's further activity. The coagulation cascade is the aspect of clotting function most often studied in our medical schools, but because of the cascade's outward complexity, many physicians limit their deeper understanding of coagulation.

The coagulation cascade is classically taught to be two separate protein systems eventually coming together in a final common pathway. The proteins involved are present in their soluble form circulating in the plasma. All are formed by the hepatocytes, except for factors V and VIII. The production site half-lives and common names for the coagulation cofactors are listed in Table 2.

The extrinsic pathway is activated by exposure to tissue thromboplastin (factor III). When blood comes in contact with factor III, factor VII is activated. Calcium and tissue phospholipids must be present for the activation to take place. This phospholipid may be

Table 2. *Plasma Protein Coagulation Factor Activities*

FACTOR	SYNONYM	MOLECULAR WEIGHT	PRODUCES	PLASMA LEVEL (mg%)	$t_{1/2}$ (h)	MINIMUM LEVEL FOR NORMAL HEMOSTASIS (%)
I	Fibrinogen	340,000	Hepatocyte	200–250	120	50–100
II	Prothrombin	70,000	Hepatocyte, vitamin K dependent	100	100	40
III	Tissue thromboplastin	45,000	Tissue			
V	Labile factor proaccelerin	330,000	Hepatocyte	5–12	25	5–10
VII	Stable factor proconvertin	55,000	Hepatocyte, vitamin K dependent	1	5	5–10
VIII	Antihemophilic factor von Willebrand factor	1–2 million	Endothelial cells, megakaryocytes, ? platelets	7	10	30
IX	Christmas factor	57,000	Hepatocyte, vitamin K dependent	4	20	30
X	Stuart Prower factor	59,000	Hepatocyte, vitamin K dependent	5	65	8–10
XI	Plasma thromboplastin antecedent	160,000	Hepatocyte	4	65	20–30
XII	Hageman factor	80,000	Hepatocyte	29	60	0
XIII	Fibrin stabilizing factor	300,000	Hepatocyte or platelets	10	150	1

supplied by the platelet membrane. Once activated, factor VII converts prothrombin to thrombin, thereby triggering the eventual formation of fibrin. The activation of the extrinsic coagulation cascade can expand the cascade by branching activity at factors VIII and V. Similarly, some of the serine proteases from the intrinsic pathway may cause factor VII to become activated. Therefore, contemporary understanding is that factor VII functions as a key branching point for the entire protein cascade system.

The intrinsic cascade is triggered by the exposure of plasma to collagen present in the vascular subendothelium. Therefore, factor XII (Hageman factor) is stimulated, and it acts as a protease to form activated factor XI. Subsequent serine proteases cleave large inactivated proteins, eventually leading to the conversion of prothrombin and the activation of the final common pathway.

Factors II, VII, IX, and X, known as the vitamin-K–dependent factors, contain a unique amino acid (γ-carboxyglutamic acid) that is essential for the attraction of the coagulation cofactors to the surface of the *activated* platelets. Vitamin K is required for the intrahepatic conversion of glutamic acid into γ-carboxyglutamic acid.[6, 52]

The final common pathway begins with the activation of prothrombin by either the intrinsic or extrinsic pathway. Calcium is required for the assembly of a macromolecular complex of thrombin, factor V, and calcium. The platelet membrane again plays a vital role as this complex must be assembled on the surface of activated platelets. Thrombin activation may be a slow process, but again it serves as a branching point, and once activated, it causes the following reactions: (1) conversion of fibrinogen to fibrin, (2) activation of factor XIII (fibrin-stabilizing factor), (3) enhancement of factor V and VIII activity, (4) initiation of fibrinolysis, and (5) further platelet aggregation. Fibrin strands are initially interconnected with weak hydrogen bonds, but once factor XIII is activated, covalent sulfur bonds are created, further strengthening and stabilizing the total clot.

Activation of the coagulation cascade serves to create plasma reactions that have physiologic action much further reaching than clot function alone. Factor XII, when activated, causes the production of kallikrein, bradykinin, and complement. Prekallikrein (Fletcher factor) is converted to kallikrein, which further reacts with low-molecular–weight and high-molecular–weight kininogens. The kinins generated may end up as kallidin and bradykinin, which (1) increase vascular permeability, (2) contract smooth muscle, (3) dilate small blood vessels, (4) induce inflammation, (5) cause pain, and (6) cause the release of prostaglandins. The complement system, a complex cascade made up of at least 22 plasma proteins, causes cell membrane lysis of antibody-coated cells. Both factor IX and the fibrinolytic system serve as triggers for the complement system.

The fibrinolytic system is immediately activated when coagulation itself is triggered. It functions to reestablish flow in vessels and works with the protein cascade to actually maintain homeostasis. The plasma enzyme plasminogen is activated by a number of substances

Table 3. *Coagulation Activity of Blood Products*

TYPE	VOLUME (mL; average)		COMMENT
Fresh frozen plasma	250–300	91% water; 7% protein; 2% carbohydrate; lipids	All coagulation proteins present
Single-donor plasma	200–250	Deficient in factors V and VIII	
Cryoprecipitate	10–15	250 mg fibrinogen; 50% of factor VIII present in fresh frozen plasma; 20%–30% of factor VIII present in fresh frozen plasma	
Platelet	50–70	5.5 × 10^{10} platelets	
Whole blood	450–500	50% decrease in factor VIII at 24 h after draw; 30% by 48 h after draw	

and is converted to the active form, plasmin. Plasmin is an endopeptidase and it can cleave either fibrin or fibrinogen. The enzyme cannot distinguish between the two molecules. Early breakdown products are known as the x and y fragments, whereas later byproducts are the "D-Dimer" and E fragments. Their distinction is important as they can cause increases in vascular permeability and depress the activity of serine proteases, thereby functioning as anticoagulants. Plasmin further depresses the coagulation cascade by degrading factors V and VIII, and it further amplifies the activity of kinins, bradykinins, and complement.

Although complex, a working knowledge of the coagulation system is easily obtainable (Table 3). The previous summary is not exhaustive and will, hopefully, act as a review for many readers. The role of the platelets cannot be stressed too heavily. Most reactions in the coagulation cascade either require the presence of phospholipid or take place on the surface of *activated* platelets. Therefore, when studying coagulation function, the physician must consider the interaction and activity of all subprocesses.

PREOPERATIVE AND INTRAOPERATIVE COAGULATION ABNORMALITIES

The abnormalities that occur preoperatively in the coagulation cascade can be intellectually categorized into those affecting one of three areas: (1) platelets, (2) the protein cascade, and (3) clot lysis. Preoperative quantitative platelet (thrombocytopenia) abnormalities may be caused for a number of reasons. An extensive patient history will be most helpful in discerning a past platelet abnormality, which most often presents as petechial hemorrhages of the mucous membranes and skin. Also, abnormal menstrual bleeding, epistaxis, and, occasionally, gastrointestinal hemorrhage may be noted.[52] However, deep tissue bleeding as seen in hemophilia is not the rule.

Thrombocytopenia may be caused by either the failure of bone marrow production or increased peripheral destruction but most commonly, when it occurs perioperatively, is caused by hemodilution.[46, 50, 66, 71] Megakaryocytic production of platelets may be depressed in syndromes where bone marrow stem cells are affected. However, sometimes thrombycytopenia may antedate the depression of leukopenia or aplastic anemia.[22, 23] Patients who have undergone chemotherapy, particularly with mitomycin C or the nitrosourea agents, are particularly susceptible to depression of production.

Many viral infections can cause bone marrow depression with resultant thrombocytopenia. Some of these viral infections may otherwise be expected to be of low virulence and self-limited.[22, 73] Drugs, particularly hydrochlorothiazide and ethanol, can depress platelet production. Alcoholic liver disease has much further-reaching coagulation disorders; however, a subset of alcoholics do experience thrombocytopenia without frank cirrhosis.

The peripheral destruction of platelets may be caused by splenomegaly, diffuse intravascular coagulation (DIC), hemolytic anemia syndrome, thrombotic thrombocytopenic purpura, and chronic heparin administration. Typically, thrombocytopenia may occur 1 to 2 weeks after chronic heparin administration. Intravenous, subcutaneous, and heparin flush administrations have all been implicated in platelet destruction. The immune-mediated nature of this platelet destruction is supported by evidence of an increase in platelet-bound IgG in patients with heparin-induced thrombocytopenia.[7, 31, 32]

Other thrombotic thrombocytopenic syndromes may be seen after viral infections. Idiopathic thrombocytopenic purpura may lead to profound platelet destruction. Steroidal therapy may be useful; however, patients may occasionally require splenectomy, therefore presenting to the operating room.[19]

Dilutional thrombocytopenia is by far the most common platelet abnormality encountered in the operating room. Acute hemorrhage with subsequent volume reexpansion may lead to such a decrease in circulating platelet number. In hemorrhage, profound levels of blood loss and hemodilution may be reached before severe thrombocytopenia becomes a problem. Platelet counts below 50,000 to 100,000/μL are considered below the acceptable level for elective surgeries. However, patients with leukemia and other myeloproliferative disorders may experience levels lower than 20,000 μL before spontaneous hemorrhage occurs.

Thrombocytopenia is the first defect encountered intraoperatively with acute hemorrhage that can contribute to a further coagulopathy or bleeding diathesis. However, for routine cases undergoing slow hemorrhage, up to 80% of the blood volume may be euvolemically lost before coagulation changes are noted.[66] The fate of platelet number and function during and after cardiopulmonary bypass has been extensively studied. Crystalloid priming of the bypass machine, plus consumption of and change in function of platelets by the pump oxygenator, roller pumps, and tubing, causes a thrombocytopenia that may be a very common cause of postcardiopulmonary bypass coagulopathies.[1, 9, 21, 27, 40, 41] Extensive reviews on this complex subject exist, and the reader is referred to them.

Dysfunctions of the protein cascade preoperatively may be caused by liver disease, genetic absence of coagulation factors, diffuse intravascular coagulation, drug-induced fibrinolysis, and the presence of paraproteins acting as anticoagulants.

As stated previously, most coagulation proteins are synthesized in the hepatocyte. When liver failure does occur, the deficits of vitamin-K–dependent factors and fibrinogen may have the greatest effect on coagulation dysfunction. When fibrinogen levels fall below 150 to 200 mg/dL, abnormal coagulation function may occur.[1, 39] The other protein procoagulants may provide normal coagulation function if present in concentrations of 30% of normal or greater.

Patients with end-stage liver disease often present to the operating room for a number of procedures: liver biopsy, hepatic resection of tumors, splenectomy, shunt procedures for esophageal bleeding secondary to portal hypertension, and, recently, liver transplantation. The prothrombin time and fibrinogen levels are useful as markers of hepatocellular synthetic function.

Of the genetic defects in coagulation factor synthesis, hemophilia A is not uncommon and has been widely publicized. Its occurrence in the male population has been estimated to be approximately 1 in 100,000.[36] Hemophilia A is a sex-linked hereditary disease characterized by decreased factor VIII-C activity. Hemophiliacs may be treated with factor-specific, concentrated, or purified factor VIII. Cryoprecipitate has been used to treat these patients as well, and it contains 80 to 120 U of factor VIII-C, 0.5 g of protein, 250 mg of fibrinogen, and 45 mg of fibronectin.[37, 52] For patients who are actively bleeding with hemophilia, 3.5 bags of cryoprecipitate per 10 kg of body weight may be necessary to arrest bleeding. When purified factor VIII preparations are used, a loading dose of 30 U/kg may be required. Each vial contains approximately 25 U of active factor VIII-C.

1-Deamino-8 arginine vasopressin (DDAVP) can produce a marked increase in circulating factor VIII activity, at least transiently.[57, 58] DDAVP has been shown to be useful in treating von Willebrand's disease, thereby decreasing intraoperative bleeding. It appears to also be effective in treating intraoperative uremic hemorrhage. Loading dosages of 0.2 mg to 0.4 mg/kg have been used with very few hemodynamic side effects. Chronic use may cause renal water and sodium retention. DDAVP usage during open heart surgery is controversial and will be discussed later in this article.

Christmas's disease is a sex-linked recessive coagulopathy with an occurrence of about 1 in 100,000 persons.[48] Its decrease in factor IX activity of 25% or less leads to hemorrhagic tendencies. Prothrombin complex concentrates may be used for treatment, as they contain large quantities of factor IX.[54] Other isolated occurrences of individual coagulation protein abnormalities do occur, but these are extremely rare. Again, a good patient history will discern a bleeding tendency. Bleeding from coagulation protein dysfunctions is characterized by spontaneous intramuscular, joint, gastrointestinal, and intracranial hemorrhage. Most often, such cases are extensively evaluated prior to elective surgery. For complex and unique abnormalities, a hematologist's consultation for intraoperative coagulation cofactor replacement would seem appropriate.

Diffuse intravascular coagulation is a consumptive coagulopathy that can occur at any of the perioperative periods; DIC can be caused by tumor destruction, sepsis, hypotension, obstetrical complications, fat embolism, and mismatched blood administration.[11, 48] It may be either compensated or decompensated, and it is characterized by the consumption of platelets, fibrinogen, and cofactors, specifically II and VII. In the most severe cases, DIC may cause extensive capillary thrombosis and organ hypoperfusion, acidosis, and death. Decreased levels of the coagulation precursors contribute to a hemorrhagic diathesis, which may be further worsened by secondary fibrinolysis. Treatment of DIC involves removing the inciting cause and supplying the patient with adequate coagulation precursors. Systemic heparinization can be used to decrease the process; however, its usage is controversial unless hypoperfusion, acidosis, and impending demise is present.

Primary fibrinolysis is often very difficult to discern from secondary fibrinolysis and DIC. Primary fibrinolysis, however, is caused by plasminogen activation, which may be seen in end-stage liver disease, liver transplantation, and cardiopulmonary bypass.[55] Today, streptokinase and tissue plasminogen activator (TPA) therapy may be used in acute arterial insufficiency and myocardial infarctions.[23] Patients may come to the operating rooms for myocardial revascularization immediately or shortly after failed TPA therapy. Reversal of plasminogen activation or prevention of it may be accomplished by the administration of ε-aminocaproic acid or tranexamic acid. Plasminogen activation may be transient as during the anhepatic phase of liver transplantation or during and immediately after cardiopulmonary bypass.[4, 30] It is important to distinguish DIC from primary fibrinolysis, as inappropriate utilization of ε-aminocaproic acid in DIC may shift a compensated DIC into a decompensated one, therefore producing a life-threatening event.

COAGULATION MONITORING

Routine coagulation monitoring has centered on those tests that are automated, inexpensive, and therefore easily performed. Such tests have functioned as a screening mechanism for identifying some coagulopathies.

Testing for platelet activity can be subdivided into tests of numbers and function. Platelet count is routinely obtained from an automated laser counter. Adequate platelet number does not infer normal activity, as platelet function may well be impaired. Tests for platelet function may be quite complex. A template bleeding time is a gross test of initial platelet function. It is simple, but it should be performed by a technician who routinely analyzes the test. It is not often used in the operating room, as anesthesiologists and surgeons do not routinely perform the test themselves, and technicians are not always available to come to the operating room.

Complete in vitro platelet function studies can be performed if a platelet function abnormality needs to be characterized.[10] Their usage is limited strictly to the preoperative and postoperative periods because they are very time and labor intensive. No single platelet function study alone may suffice. Gas retention, ADP, collagen, epinephrine, thrombin, serotonin, and ristocetin agglutination tests should be performed for a thorough evaluation. Since such tests require a considerable amount of a technician's time, they are very underutilized, and it is impractical to use them intraoperatively. Unfortunately, if clinical bleeding occurs intraoperatively, the routine testing for platelet function leaves a major vacuum in our ability to monitor coagulation.

The protein coagulation cascade has been screened by the prothrombin (PT) and partial thromboplastin time (PTT). Both are performed on centrifuged plasma in a laboratory setting. The PT is a screening test for the extrinsic pathway activity and therefore examines the vitamin-K–dependent factors II, VII, IX, and X. To perform the test, plasma is activated by adding thromboplastin and calcium, and the time until gel formation is noted. Normal values are 12 to 14 seconds and should be checked for each laboratory doing the test. The PT is most useful for following patients either with vitamin-K–dependent abnormalities (patients on chronic antibiotics or bowel preparations) or those receiving dicumarol therapy.[60]

The PTT again functions as a screening test that is performed in vitro using isolated plasma. It is a test for the intrinsic cascade and is performed by adding a commercially available cephaloplastin (a mixture of platelet phospholipid substitute, kaolin, and cellite). Again, time until initial fibrin formation is noted; normal values should be less than 35 seconds. It has been the standard test for partial heparinization and for decreased levels of factors XII, XI, IX, and VIII and those in the common pathway. Levels as low as 30% to 40% of normal coagulation factors will still produce normal coagulation function and normal PT and PTT tests.[60]

The thrombin time is a screening test to assess the final common pathway. Again, isolated plasma is used as a substrate, and it is activated by adding exogenous thrombin. Time to fibrin formation is noted, with normal values being less than 15 seconds. If the thrombin time is abnormal due to the presence of fibrin-split products, inhibitors, or heparin, a somewhat more obscure test, the reptilase time, may be helpful. Reptilase, an enzyme extracted from viper venom, stimulates the final common pathway and is not affected by the factors just noted.

Individual factor levels may be tested if unusual genetic abnormalities are suspected. Fibrinogen levels may be also grossly quantified using plasma dilutions.

Many of these tests are now automated, and recent technologies have been developed that miniaturize the testing and have made it available at the bedside. The argument that it takes too long to get a PT or PTT for the results to be useful is no longer valid. However, these screening tests do have some major limitations. They do *not* examine the all-important interaction between the platelets and the coagulation cascade; therefore, it is more than theoretically possible to have normal PTs and PTTs and still have very active bleeding due to coagulopathies. A screening PT and PTT will do very little preoperatively to predict bleeding that cannot be foretold from a good history. Routine ordering of these tests for elective surgery in most patients is probably a waste of money and provides a relatively small amount of information. Furthermore, it is not necessarily prudent to transfuse factors based solely on an abnormal screening test. Other articles discuss the risk of blood transfusion and, specifically, the indications for fresh frozen plasma or cryoprecipitate transfusions. There are no studies that directly correlate abnormal PTs and PTTs with the quantity of surgical blood loss. Indeed, recent work in some situations shows the tests have no predictive value for bleeding.[64, 66]

Fibrinolysis may be primary or secondary due to DIC. The diagnosis of early clot lysis may be gained from the euglobulin lysis time. Plasma minus the globulin fraction is stimulated to clot and the time to clot dissolution is noted. Times of greater than 120 minutes are reported as normal. Normal fibrinogen levels must be present for this test to have meaning. It is one of a large battery of routine tests that may be helpful in discerning DIC from primary fibrinolysis.

The presence of fibrin degradation products may be grossly quantified by a bioassay, with normal values being less than 10 mg%. Their presence signals an ongoing lytic process as the reticuloendothelial system and a normally functioning liver will clear them ($t\frac{1}{2}$ = 7.5-9.5 hours). Even if both of these tests show positive results, DIC and primary fibrinolysis must be discerned by clinical suspicion and the examination of the fibrinogen levels, platelet number, and levels of other consumable coagulation proteins (II, VII, and X).

Soluble fibrin monomer complex may be detected and is helpful in discerning DIC and primary fibrinolysis. It is formed when thrombin cleaves fibrinogen, creating fibrin monomer, which normally forms a weak hydrogen bond except in the presence of fibrin degradation products.[37] The soluble fibrin monomer can actually undergo coagulation with ethanol, protamine, or cooling. The presence of soluble fibrin monomer is seen in DIC patients, some cases of acute myocardial infarction, deep venous thrombosis, and pulmonary emboli. Still, however, there is a 10% false-negative incidence of soluble fibrin monomer in DIC.[29]

The activated clotting test (ACT) is the most widely used intraoperative coagulation test for heparinization in cardiopulmonary bypass. It is simple, inexpensive, and easy to perform. A sample of whole blood placed in a rotating test tube with a magnet inserted is activated by diatomacious earth or cellite. When initial fibrin formation occurs, the magnet is enmeshed and the machine signals clot formation. The ACT, therefore, does look at whole blood clotting, but essentially notes only the time to initial formation of fibrin. The ACT has proved to be useful for gross testing of heparinization and reversal; however, it is notoriously variable under certain conditions.[12, 18, 31, 35, 72] Temperature and hemodilution both affect it. The literature is replete with articles demonstrating inaccuracies of the ACT. It has no predictive value for postoperative hemorrhage in patients undergoing cardiopulmonary bypass. However, the ACT continues to be used extensively because it is easy and inexpensive.

WHOLE BLOOD VISCOELASTIC TESTS

Ultimately, the surgeon and anesthesiologist would like to know which patient's blood will clot, how fast it will clot, and whether that clot will behave normally or break down. Two tests of whole blood clot strength (viscoelastic tests) have gained recognition in the literature. These tests are the Thromboelastograph (TEG, Haenoscope, Park Ridge, IL) and the Sonoclot (Sienco, Denver, CO).[28, 56, 59, 61, 64, 65, 66, 74] Both tests examine the interreaction of platelets with the protein coagulation cascade from the time of initial fibrin platelet interaction, through platelet aggregation, clot strengthening, and crosslinking, to eventual clot lysis. These tests simply view clotting on a gross level, testing clot strength over time.

The TEG uses a rotating cuvette heated to 37°C into which a metal piston is suspended. As the fibrin forms between the wall of the cuvette and the piston, a mechanical link is formed, which then transfers that energy and creates a characteristic tracing. Measurements of defined parameters for the onset of clot formation (R value), the speed of fibrin/platelet interaction (α and K values), the maximum clot strength (MA), and the clot strength 60 minutes later (A_{60}) are routinely measured. A schematic of normal and abnormal values has been established and published. Using this key, a number of coagulopathies may be discerned to guide coagulation therapy.

The TEG was initially introduced intraoperatively with liver transplantation procedures, where it is believed to be useful by some anesthesiologists.[30] It has also been used in cardiopulmonary bypass. The TEG is a much more effective predictor of postbypass hemorrhage than is either the ACT or routine coagulation testing.[64] This is almost certainly due to the fact that the TEG examines clotting function as a gross interaction of all the components rather than each component function. In cardiopulmonary bypass, platelet dysfunction is one of the most common causes of coagulopathy. As discussed earlier, there is a monitoring gap for platelet function in our previous coagulation monitors.

The TEG has been shown to detect platelet function differences stimulated by DDAVP and has been shown to diagnose and guide treatment of intraoperative fibrinolysis.[61, 65] The acute coagulation changes caused by hemodilution and intraoperative hemorrhage demonstrate coagulation changes consistent with dilutional thrombocytopenia as diagnosed by the TEG. Diffuse intravascular coagulation and primary fibrinolysis, at least in an animal model, may be discerned by one test, the TEG, whereas routine monitoring requires an extensive battery of tests to differentiate these coagulopathies.[62]

Hypercoagulation can be diagnosed by the TEG. This capacity makes the TEG useful both as an experimental tool with which to investigate this understudied condition and also as a monitor for diagnosing venous and arterial thromboses.

Recent pilot studies have shown that the TEG may be able to follow coagulopathy development during full-heparinized bypass by adequately activating blood samples with cellite before adding them into the TEG. It appears, at least to this author, that the TEG is a most valuable tool for intraoperative coagulation monitoring and management.

The Sonoclot is a similar device that operates by a vibrating piston in a cuvette, as opposed to the rotating cuvette and stationary piston used in the TEG. The Sonoclot measures changes in blood viscosity within a very small distance from the vibrating probe. Like the TEG, it examines whole blood viscoelastic properties and, therefore, shares all the advantages when compared with routine coagulation testing. The Sonoclot has been shown to be particularly sensitive to platelet abnormalities and, in side-by-side tests with the TEG, is shown to be equally predictive of postcardiopulmonary bypass hemorrhage.[66] Further work with the Sonoclot for development of parameters and schematic diagnostic tools is necessary for easy coagulopathy identification. Certainly, both methods of whole blood testing are viable, inexpensive, and relatively rapid methods of assessing clot function in the operating room. Should the results of these tests be abnormal, further in-depth testing may be warranted if a coagulopathy is not identified to the satisfaction of the clinician.

TREATMENT OF COAGULOPATHIES

The days of "shotgun" therapy for coagulopathies have ended. No longer can we transfuse a menu of blood products in the hopes that a defect can be remedied. "Cookbook" approaches that advocate the administration of fresh frozen plasma for a given number of units of red blood cells can no longer be tolerated. Testing must first identify real deficiencies and only then can treatment be instituted. A recent study comparing recipe-guided platelet and fresh frozen plasma administrations during massive hemorrhage showed no difference in bleeding, units of blood transfused, hematocrit, PT, PTT, or thrombin time in any group.[53]

The previous discussion has noted the attributes of a number of tests. Dilutional thrombocytopenia and, eventually, dilutional hypofibrinogenanemia are the most common hemorrhagic coagulopathies. Hypocalcemia secondary to rapid transfusion does not often occur outside of liver transplantation. If it does, it most certainly causes cardiac dysfunction before coagulation dysfunction.

Our ability to treat coagulopathies remains rather limited. Besides giving individual isolated factors for known genetic defects, the treatment of coagulopathies is with fresh frozen plasma, cryoprecipitate, and platelet transfusions. Table 2 notes the relative amounts of factors present in transfusion products.

Platelets are obtained from either whole blood or are harvested in platelet phoresis from individual donors. Each phoresis harvests platelets equal to the number obtained from five to eight whole blood donations. Platelets are stored at 20°C to 24°C for up to 5 days, at which time they are outdated because of the increased risk of sepsis. One bag of random-donor platelets should contain 5.5×10^{10} platelets in 50 to 70 mL of plasma. One unit of platelets usually increases the platelet count after transfusion by 5000 to 10,000 mL. How active those particular platelets are and their half-life depends on the length of their storage time.

DDAVP has been mentioned previously as a drug that can increase the levels of von Willebrand factor C (VIII-C) and increase platelet function in uremia. It has had a controversial record so far in cardiopulmonary bypass hemorrhage. Initial studies showed decreased postoperative blood loss, both in cardiac and spinal surgery, but more recent studies have not been able to replicate those findings.

ϵ-Aminocaproic acid is effective in stopping the conversion of plasminogen to plasmin. Recent studies have shown decreased hemorrhage after cardiopulmonary bypass utilizing ϵ-aminocaproic acid. However α-aminocaproic acid may be dangerous in the presence of DIC. Its universal use as an anticoagulant cannot be advocated. Only careful monitoring to determine the specific cause of a coagulopathy can result in the use of the proper remedy in the operating room.[20, 63] Other antiplasminogen compounds, such as tranexamic acid, appear promising, and aprotinin holds particular appeal.[2, 24] Aprotinin appears to block the effects of bradykinins, complement, and plasminogen activation during cardiopulmonary bypass. In several early reports, hemorrhage has been significantly reduced following the use of adequate dosages.

SUMMARY

Hemorrhage either may be caused by coagulopathies or be the result of them. The present climate of blood transfusion medicine dictates that each unit transfused be utilized judiciously. While coagulation and its monitoring may appear complex, an understanding of its operation and functions is necessary in order for the operating room team to make these decisions. A push for consistent use of up-to-date coagulation monitoring, technology, and research has been solely lacking in operating teams today. Applying the latest principles of coagulation and its monitoring, as outlined in this article, on a case-by-case basis, will help to minimize hemorrhage in operating rooms during the 1990s.

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Risks of Transfusion

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For the four decades preceding 1984, the medical community had known about, and given scant clinical credence to, the many risks to recipients of transfused blood and blood products. The most common of these risks had been febrile and urticarial reactions associated with only minor morbidity. Major morbidity and mortality from transfusion-associated sepsis, viral infection, and clerical errors had been sufficiently rare that few in the medical community, despite admonitions of transfusion specialists, had altered their clinical practices to decrease these risks.

The transition from a low level of interest in risks of transfusion to accelerated interest and dramatic changes in transfusion practices was abrupt. It was precipitated by the epidemiologic linkage of acquired immunodeficiency syndrome (AIDS) to transfused blood and blood products in 1984. The medical community, provided evidence of infective risks of transfusion and swept by the wave of public concern for safety, responded rapidly by altering transfusion practices. Blood banking programs, supported by major advances in detection of infectous agents or the identification of associated markers, were soon able to provide and document a very safe supply of blood and blood products.

Clearly, these responses have been impressive and have mollified public concerns of the safety of blood transfusion. The risks of transfusion continue, however, and this article reviews various hazards related to the transfusion of blood and blood products. These hazards will be discussed in three general categories: (1) disease transmission, (2) immune-mediated transfusion reactions, and (3) immunosuppression and immunologic pathologies. We will not discuss risks due to

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the mechanics of transfusion (e.g., air embolism and fibrin deposition).

DISEASE TRANSMISSION

The risk of infectious complications was recognized with the increasing use of homologous blood and blood products in the 1930s. Transfusion-associated hepatitis, marked by jaundice, was reported in 1943.[11] Since then, many infective agents, including viruses, bacteria, spirochetes, and parasites, have been identified.

Viruses

Hepatitis. The most frequent major morbidity attributable to transfusion of blood products is viral hepatitis.[1] There are currently at least four recognized types of viral hepatitis: hepatitis A (HAV); hepatitis B; non-A, non-B hepatitis (NANB), or hepatitis C virus; and delta hepatitis. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as other rare viruses, may also be associated with transfusion-induced hepatitis. Although there has been much progress in identification of these viral agents and their specific clinical effects, our understanding of them is still unsettled and evolving.

Hepatitis A. Hepatitis A is caused by a small RNA virus, hepatitis A virus (HAV), that is usually transmitted by fecal contamination. The disease, formerly known as infectious hepatitis, is usually mild and self-limiting. Because there is a very brief period of antigenemia of low titer and no chronic carrier state, the HAV is only rarely implicated in transmission by blood products.[65, 109] The currently available IgM anti-HAV identification assay is both sensitive and specific, with rare false-positive results.[66]

Hepatitis B. Hepatitis B is caused by a small DNA virus, hepatitis B virus (HBV), that is transmitted primarily through blood contamination, but it can also be transmitted perinatally and through sexual contact. Hepatitis B and NANB hepatitis are responsible for the vast majority of post-transfusion hepatitis cases. The HBV has distinct antigens that allow its identification. There is a surface protein coat (HBsAg—formerly called the Australian antigen) and an inner core that contains core antigen (HBcAg), a soluble protein component of the core called "e" antigen (HBeAg), and a specific DNA polymerase.

Detection of antibodies to HBV antigens, as well as direct identification of some of the antigens, has markedly decreased the occurrence of post-transfusion HBV in the United States.[7] Less than 10% of post-transfusion hepatitis is now caused by HBV.[2, 8, 57, 107] The Association of American Blood Banks recommends that all donated blood products be tested for HBsAg, antibody to HBcAg, and alanine aminotransferase (ALT) (Table 1). When used alone and in areas where HBV infection is endemic, identification of HBV infection with HBsAg may be falsely negative in up to 70% of donors carrying HBV.[78] The test is much more reliable in areas where HBV infection is not

Table 1. *Routine Tests On Donated Blood*

- ABO and Rh type
- Screen for antibodies to red blood cell antigens
- Infectious diseases
  - Serology for syphilis (VDRL)
  - Hepatitis B surface antigen (HBsAg)
  - Antibody to hepatitis B core antigen (anti-HBcAg)
  - Antibody to hepatis C virus
  - Antibody to HIV-1
  - Antibody to HTLV-I/II
  - Serum ALT

Abbreviations: HIV = human immunodeficiency virus; HTLV = human lymphotrophic virus; VDRL = Veneral Disease Research Laboratory.

endemic.[44] The addition of anti-HBcAg[31] and ALT testing, suggesting previous HBV or NANB hepatitis infection, has made identification of blood contaminated with HBV more specific and has been associated with a decrease in the incidence of transfusion-associated hepatitis. Also playing roles in decreasing the incidence of transfusion-associated hepatitis are the self-deferral and exclusion questionnaire programs of the blood banks. Worthy of note, anesthesia and other health care personnel that handle blood and secretions have increased HBV seropositivity.[13, 53]

Non-A, Non-B Hepatitis. Prior to the routine testing of donated blood for HBsAg, less than 30% of post-transfusion hepatitis patients were found to be positive for HBsAg.[1] With the introduction of routine donor blood testing for HBsAg, this rate dropped to less than 10%.[2, 8, 57, 107] It became clear that an agent or agents other than HAV and HBV were responsible for most post-transfusion hepatitis cases.[39] With no specific agent identified, the agent was considered to be the NANB hepatitis virus.

The post-transfusion hepatitis of NANB virus differs clinically from that of HBV. In general, HBV is associated with an acute icteric illness, with up to 10% of patients progressing to chronic carrier states, and one quarter of these developing histologic chronic active hepatitis or cirrhosis.[28] In contrast, NANB hepatitis is usually mild; patients are usually asymptomatic and anicteric.[40] It occurs after a mean incubation period of 7 to 8 weeks, with 80% of cases occurring between 5 and 12 weeks after transfusion. However, greater than half of NANB hepatitis cases progress to chronic disease states. In 1987, approximately 48,000 patients developed acute post-transfusion NANB hepatitis. Over half of these became chronically infected. It is estimated that 6000 of these patients will have chronic active hepatitis, and 2400 will have cirrhosis.[139]

Hepatitis C. Preliminary studies of hepatitis C virus (HCV) suggest this virus to be responsible for at least some of the NANB post-transfusion hepatitis cases.[77] Specific assays for antibodies to HCV are being developed, and further studies will determine what percentage of cases currently classified as NANB hepatitis are associated with HCV infection. In April 1990, the US Food and Drug Administration approved commercial distribution and use of tests for antibody to HCV. In the absence of a specific NANB hepatitis marker other than antibody to HCV, surrogate (indirect) tests are used to detect NANB hepatitis carrier blood donors.[40] Strong associations have been noted between recipient NANB hepatitis and the presence of anti-HBcAg and elevated ALT in donor blood.[3, 8, 76, 117] The use of these two tests together became routine in 1987 and, combined with improvements in self-deferral practices, has been associated with a 40% decrease in the incidence of post-transfusion NANB hepatitis.[118]

Delta Virus, Cytomegalovirus, and Epstein-Barr Virus. These three viruses are variably associated with post-transfusion hepatitis, and they often occur in special circumstances. Delta virus is a defective RNA pathogen that can replicate only in the presence of replicating HBV (co-infection).[105] It is highly pathogenic and either causes or aggravates HBV-associated liver disease, increasing the risk of fulminant liver failure and mortality from acute hepatitis.[89]

Although present in most donated blood products, CMV and EBV are rarely pathogenic after transfusion.[5, 56, 101, 125, 136] Most transfusion recipients are already immune to these two viruses, and most donors have neutralizing antibodies that provide passive protection. CMV, particularly, can cause serious morbidity in immunosuppressed recipients.[4, 18, 59, 83] For example, it may cause pneumonia, hepatitis, or symptoms of graft rejection in immunosuppressed adults.[23, 76, 86, 104] In neonates, it may be associated with atypical lymphocytosis, hepatosplenomegaly, and pneumonia.[6, 12, 57] In general, CMV seronegative blood is used in neonates who are born to CMV-negative mothers and who weigh less than 1200 g at birth. Seronegative blood is also used in seronegative transplant recipients who receive seronegative organs or marrow.

Because most donated blood has CMV, it is not practical to screen all donated blood for CMV. Screening assays for antibodies to CMV are usually performed on blood products for neonates or CMV-negative transplant patients. CMV may be present in any blood products that have granulocytes. Unfortunately, any red blood cell (RBC) products, even those that have been frozen and deglycerolized or washed to be leukocyte-poor, may transmit CMV infection.[126]

Retroviruses. *Human Immunodeficiency Virus, Type 1.* Within a year of the first report in 1981 of opportunistic infection and Kaposi's sarcoma in homosexual men,[30] *Pneumocystis carinii* pneumonia was reported in three hemophilic patients who had no risk factors other than their use of factor VIII concentrates.[29] Shortly thereafter, Amman et al[9] reported an infant who received multiple transfusions and developed pneumocystis pneumonia. One of the donors of blood to this child later developed the same infectious process. Subsequently, the association of blood transfusions and transmission of AIDS became evident.[70]

Although the etiologic agent of AIDS was unknown at the time, the Association of American Blood Banks called for self-deferral from donating by members of high-risk groups in March 1983.[26] The independent identifications of the presumptive etiologic agent, human immunodefiency virus, type 1 (HIV-1, formerly human lymphotrophic virus, type III [HTLV-III] and lymphadenopathy-associated virus [LAV]) by Montagnier[10] and Gallo[54] in 1983 and 1984, respectively, and the development of serologic tests for antibody to HIV-1, led to evaluation of effective heat treatment techniques of pooled blood products in November 1984[24] and donor screening of all blood products in April 1985.[27] These key events effectively improved the safety of the US blood supply.

Although the number of reported transfusion-related AIDS cases in the United States rose from 256 in 1985 to 4051 by November 1989, the majority of these cases were traced to blood products received prior to the routine screening of blood donors in 1985.[133] Routine testing of donated blood and modified donor exclusion criteria, plus minor improvements such as the confidential donor exclusion option given to all donors since October 1986, has been highly effective in eliminating HIV-1–infected blood products from the nation's blood supply. Nevertheless, HIV-1 infections have followed transfusion of blood products that have been negative for antibody to HIV-1 (anti–HIV-1). Ward et al[134] reported 13 recipients of seronegative blood (from seven donors) who developed detectable anti–HIV-1. This study and several others suggest the risk of being infected from a seronegative unit is between 1 in 35,000 and 1 in 86,000.[75] Definitive studies on the risk of HIV-1 acquisition from seronegative blood are currently being conducted on women without known risk for HIV-1, the lowest risk group that can be identified.

The safety of the blood supply from HIV-1 contamination can be improved further by asking donors very explicit and direct questions regarding their risk status. The Centers for Disease Control's HIV Blood Donor Study Group reviewed 2,153,600 blood donations from May 1988 to April 1989 from 19 transfusion centers.[96] They found that 68% of the 462 donors who had seropositive blood also had easily identifiable risk factors for HIV-1 infection, and only 5% used the confidental exclusion option. Another group in Los Angeles confirmed their findings that the majority of HIV-1–infected donors could be excluded by using simple language and more explicit questions when interviewing potential blood donors.[106]

Other factors leading to potential HIV-1 transmission need to be considered. For example, in 1985, 13 units of documented, known HIV-seropositive blood products were mistakenly transfused because of clerical errors.[138] As more tests are conducted on each donated unit of blood, the risk of clerical error rises. Numerous centers are evaluating computerized tracking systems to decrease the risk of clerical errors.

Currently, 1 in 5000 to 1 in 10,000 donors test positive for HIV-1 antibody by enzyme-linked immunosorbent assay (EIA) and Western blot immunofluorescence.[96] There is another small group with positive EIA and indeterminant Western blot test results. Although the majority of these indeterminant cases are believed to be related to HLA cross-reactivities, the Association of American Blood Banks has recommended that the blood products of these donors not be used. Recent studies that have prospectively evaluated these donors over several years have not documented that any of these potential donors have converted to EIA- and Western-blot–positive or have developed any symptoms of HIV-1 infection.[41, 90]

Improvements in laboratory identification of HIV-1 seropositive blood will make a very safe blood supply in the United States even safer. The use of recombinant nucleopeptide immunoassays, particularly those with low cost, rapid analyses, and high sensitivity and specificity, will further strengthen the safety of the US blood supply and have marked benefits in the blood supply of less developed countries.[103] Health care systems in many less developed countries do not have the resources or personnel to evaluate donated blood using the EIA and Western blot tests common to more developed countries. In addition, in countries where refrigeration is scarce and whole blood fresh within 4 hours of donation is the most commonly transfused blood, identification techniques that take minutes instead of hours will greatly improve the risk of HIV-1 seropositive transfusions.[64]

Human Immunodeficiency Virus, Type 2. In 1986, a West African with symptoms of AIDS was found to have a retroviral infection that was immunologically distinct from HIV-1.[33] The retrovirus was identified as human immunodeficiency virus, type 2 ([HIV-2], formerly HTLV-IV), a virus that is similar to HIV-1 and simian immunodeficiency virus.[43] Since that initial case report, there have been other well-documented cases of HIV-2 infection, including several in the United States.[25] In mid-1989, the Retrovirus Study Group of the French Society of Blood reported on 18 asymptomatic blood donors who were found to have HIV-2 antibodies that initially cross-reacted with HIV-1 EIA tests.[35] By studying patients who were HIV-2, seropositive and also symptomatic with AIDS, they found that most persons with HIV-2 were identifiable because their HIV-2 antibodies cross-reacted with HIV-1 EIA tests. As these persons became overtly symptomatic, the cross-reactivity was less pronounced. In the United States, HIV-2–specific tests on sera from 22,699 asymptomatic persons, including 8503 randomly selected blood donors, failed to reveal an HIV-2 infection.[25]

If potential donors who are symptomatic for AIDS are excluded, it appears at this time that HIV-1 screening tests are sufficient to identify any HIV-2 seropositive blood. As the prevalence of HIV-2 infection increases in various populations, it may be necessary to test donated blood specifically for the presence of HIV-2 or its antibodies.

Human T-cell Lymphotrophic Virus, Types I and II. In 1978, human T-cell lymphotrophic virus, type I (HTLV-I) became the first retrovirus identified in humans.[98] It is associated with the rare, highly malignant adult T-cell leukemia and also several myelopathies such as tropical spastic paraparesis. An immunologically similar human T-cell lymphotrophic virus, type II (HTLV-II) is associated with variants of T-cell leukemias and lymphomas. Because these viruses are similar immunologically, passive agglutination or indirect immunofluorescence for HTLV-I is indistinguishable from HTLV-II.[17]

HTLV-I is endemic in Japan, with 1 in 20 potential blood donors seropositive.[17] In contrast, estimates suggest that less than 25 in 100,000 of US donors are HTLV-I/II seropositive.[106, 110] Most of those donors are intravenous drug users.[95] Because routine testing for HTLV-I/II has been instituted only recently in the United States, it is unclear how easily HTLV-I/II is transmitted through transfusion of blood products. To date, there have been at least 12 reports of persons who may have acquired HTLV-I/II infection via transfused blood products. The risk of developing HTLV-I/II seropositivity and any of the rare complications associated with the viruses appears to be very low. Nevertheless, the Food and Drug Administration has recommended that blood donated for transfusion in the United States be screened for antibodies to HTLV-I/II.[71]

Bacteria

Blood and blood products, homologous or autologous, may be contaminated with microorganisms. Various microorganisms, both pathogenic and nonpathogenic, can be cultured in up to 5% of collection systems and blood products. In general, bacterial contamination of blood occurs from either a break in sterile technique during collection and processing of blood or unsuspected bacteremia in donors.[137] Contamination of blood by bacteria has been a major concern in decades past.[85, 86] The use of modern collection systems and strict standards for skin preparation, collection, and storage of blood products has reduced, but not eliminated, this risk of bacterial contamination.

In 1981, new techniques made it possible to store platelets at room temperature for up to 5 days.[63] This technique greatly increased the supply and availability of pooled platelets. Further refinement of platelet storage in 1984 extended the shelf life of platelet storage at room temperature to 7 days. This improvement was not without risk; small numbers of bacteria that may be initially present in platelets may proliferate at room temoerature.[19] From 1980 to 1983, there were nine reported transfusion-associated deaths from sepsis in the United States.[19, 63] Six deaths occurred in patients administered platelets stored at room temperature for greater than 3 days. *Salmonella* and staphylococcal species have been the organisms most often associated with platelet contamination.

Other blood products may also be contaminated with bacteria and associated with sepsis in recipients. Sepsis from *Yersinia enterocolitica* and *Pseudomonas fluorescens*, acquired from cryoprecipitate and RBCs, has resulted in several recipient deaths.[34, 55, 115, 137] These bacteria can replicate at temperatures as low as 4°C, unusual for most bacterial pathogens. Other microorganisms have been implicated in septic complications from transfusion of blood products.[131]

Spirochetes

Spirochetes, specifically *Treponema pallidum*, have a limited ability to survive at refrigerator temperatures.[69] Infectivity and survival time of treponemes is less than 120 hours. Currently, the only blood product not stored at these low temperatures is platelet concentrate (stored at 20–25°C), and it is this blood product that has the greatest risk of treponemal transmission.[128, 129]

For years, serologic tests for syphilis have been routinely performed on donated blood.[91, 102] These screening tests include cardiolipin antigen detection (Venereal Disease Research Laboratory [VDRL]) and *T. pallidum* hemagglutination assay. After screening, the seropositivity of blood is confirmed with a fluorescent treponemal antibody-absorption test. Because syphilis is so rarely transmitted, the Association of American Blood Banks no longer requires screening for syphilis. The US Food and Drug Administration, however, still requires this testing because individuals with this venereal disease may also be at higher risk of concomitant HIV infection. Transmission by transfusion of other spirochetes, including the tropical treponemal diseases of yaws and pinta, and also Lyme disease, has not been reported.[108]

Parasites

Human parasites often spend part of their life cycles in blood and may, therefore, be transmittable to the recipient of a donated blood product. Many parasites have been implicated in transfusion-associated infection, including malaria, Chagas disease, babesiosis, toxoplasmosis, filariasis, and kala-azar. In general, major morbidity or mortality from transfusion-associated parasitic infection is rare. Most parasitic endemic areas are located in underdeveloped countries. In these countries, the prevalence of the parasitic disease is high, and many transfusion recipients already have immunity to the parasite. In addition, in most of these areas, transfusion practices are limited.

However, there is concern for the importation of these diseases to developed countries and its effect on transfusion practices. For example, the incidence of malaria in Great Britain increased exponentially in the 1970s.[20] Similar increases are expected in the United States in the 1980s. As the incidence increases, so does the risk of infection from homologous blood products. In the United States, from 1972 to 1981, there were 26 blood product recipients who developed malaria, and four died.[61] Because very few organisms are required to transmit malaria, most blood products have been implicated.[22] Yet, because the number of cases in the United States is sufficiently small and predonation interview techniques eliminate almost all potential donors with previous infection or those who have traveled to endemic areas, there is no routine testing of donor blood for *Plasmodium* species.

Babesiosis is worthy of mention because of its presence in the heavily populated areas of the northeast United States, particularly southeastern Massachusetts, its islands, and rural Long Island.[21] It is a parasitic disease associated with fever, fatigue, and hemolytic anemia. The parasite is *Babesia microtia*, a protozoan that dwells in RBCs and is transmitted to humans from nymphal ticks carried by woodland rodents and whitetail deer.[58] Babesiosis has been transmitted by both platelet and RBC transfusions.[68] Currently, it is a rare problem, and routine donor screening is not warranted at this time.[100] Persons from endemic areas cannot, however, donate blood during the summer months when there is potential transmission of *Babesia* by ticks.

IMMUNE-MEDIATED TRANSFUSION REACTIONS

Prior to AIDS, the most feared consequence of blood transfusion was hemolytic transfusion reaction, leading to acute renal failure, disseminated intravascular coagulation, and death. It is still a major concern, and in most cases, reported fatal hemolytic reactions are associated with clerical errors. Since 1975, the Food and Drug Administration has required all laboratories providing blood products or blood-product–related services to report any donor or recipient fatalities. A review of this information at one decade found 58% of transfusion-related deaths to be due to hemolytic reactions.[42] Of these, 71% were from ABO incompatibilities and 26% were from antibody incompatibilities other than ABO antibodies. In nearly every case, clerical or technical human error was involved. These clerical and technical errors were primarily identification inaccuracies and performance errors during testing of blood for antibodies. Since many identification inaccuracies occurred in the operating room or intensive care setting, anesthesia personnel should be extremely vigilant to observe proper identification procedures when transfusing blood products.

Immunization, or development of immunity to antigens in homologous blood products, is stimulated by the introduction of antigens foreign to a recipient's blood. These antigens are primarily found on cells in blood products but are not necessarily related to the main cellular component of the blood product. For example, platelets and leukocytes may be found in RBC products and may provoke immune responses. Antigens in plasma, such as immunoglobulin A (IgA) proteins, can also stimulate an immune response.

Immunization to red cells is manifest most dramatically as an acute hemolytic reaction, but it may also result in delayed reactions. Delayed transfusion reactions usually are manifest only by diminished survival of the transfused RBCs, post-transfusion anemia, and mild jaundice.[97] Immunization to leukocyte and platelet antigens occurs less frequently than it does to RBCs, but it may be a major clinical problem in the care of patients with leukemia or bone marrow failure.[79] In these patients, immunization to platelets is secondary to previous platelet therapy.

Immunologic responses to leukocyte antigens are most commonly manifest as febrile transfusion reactions.[37] Although most febrile reactions are not associated with major morbidity, they do produce patient discomfort and increase hospital costs, with the need to provide leukocyte-poor products and the required clinical investigations of febrile episodes. Though rare, the major morbidity from a leukocyte immune reaction is transfusion-related acute lung injury.[132] This condition typically occurs within 6 hours of transfusion of a blood product containing a donor antileukocyte antibody, although less frequently the recipient may have an antibody to leukocytes in the donated blood product.[99] The clinical syndrome is pulmonary edema and lung infiltrates, presumably from immunologic damage to capillary-alveolar interfaces. The majority of patients with this transfusion-related injury recover with supportive therapy within 48 hours.

IMMUNOSUPPRESSION AND IMMUNOLOGIC PATHOLOGIES

Blood transfusions are associated with clinical phenomena attributed to immune suppression. Pretransplant transfusions in dialysis patients are associated with prolonged survival of subsequently transplanted kidneys. Perioperative transfusions for colorectal cancer surgery are associated with early recurrence and poor prognosis. In addition, perioperative transfusions may be associated with an increased risk of developing a postoperative infectious complication.

In 1973, Opelz et al[92] noted that renal transplant recipients who had not been transfused preoperatively had poorer survival of renal allografts than previously transfused recipients. Their observation provoked outright disbelief, but subsequent studies have confirmed their results.[14, 23, 93, 127, 130] Burrows and Tartter[23] reported that colorectal cancer patients who received intraoperative transfusions had earlier recurrence of their cancers and poorer outcomes than those who did not require blood or blood products. Their findings have also been confirmed, and multivariate analyses have failed to implicate confounding variables such as tumor size, pathologic staging, blood loss, or duration of surgery.[46, 48, 52, 120] Similar studies have documented a relationship between blood transfusions and the development of bacterial infections in trauma[36, 38, 88] and coronary artery bypass patients,[84, 94] as well as individuals with Crohn's disease[123] and colon cancer,[119, 120] whether operated on or not. These studies suggest that blood transfusions contribute to increase the risk of infection without the presence of tissue destruction or contamination.[32, 82, 121]

The immunosuppressive effects of transfusion in dialysis patients and others include significant depression of lymphocyte responses to antigens and mitogens, suppression of mixed-lymphocyte reactivity, and inhibition of cell-mediated lympholysis.[47, 74, 80, 81, 87] There are low helper/suppressor lymphocyte cell ratios and suppressed killer cell cytotoxicity.[112–114] In experimental models, cell-mediated immunity is diminished, interleukin-2 production is reduced, and plasma immunologic activity is suppressed.[49–51, 116, 135] These effects are not transient and may persist for a year or more.[122, 124]

The specific mechanism and responsible component of transfused blood has not been identified. Many cellular components may be implicated in the suppression of immune responses in experimental models.[60, 72, 73] However, plasma components have also been implicated in similar studies.[62, 67] It has been suggested that viral contamination of blood may suppress the immune response. CMV infections, for example, are associated with immune suppression, and post-transfusion infection by other infectious agents is common.[15, 16, 45]

SUMMARY

There are few alternatives to blood transfusion in clinical practice. Autologous blood transfusion is available and increasing in popularity, primarily because of patients' fears of contracting AIDS. Although many risks of transfusion may be avoided by the use of autologous blood, autologous transfusion is susceptible to many of the clerical and contamination problems of homologous blood. For patients with anemia, or those undergoing emergency or extensive surgical procedures, there is no practical alternative to the transfusion of homologous blood products. Because many transfusions are unnecessary, modification of improper transfusion practices is a logical first step to the reduction of transfusion risks.

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Trends in Transfusion Therapy

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The first blood bank was established at Cook County Hospital in Chicago in 1937. The trends in transfusion therapy since that time have been governed primarily by advances in blood bank technology, demands imposed by new medical and surgical therapies, and concerns about transfusion-transmitted disease. The federal government has also played a significant role in shaping transfusion policy.

FACTORS DETERMINING TRENDS IN TRANSFUSION

The Role of the Federal Government

Federal policymakers began to critically review the nation's blood program in the early 1970s. Responsibility for monitoring blood resources was transferred from the National Institutes of Health (NIH) to the Food and Drug Administration (FDA) in 1972. The FDA thus became the principal regulator of blood collection, processing, testing, and marketing. In 1973, a National Blood Policy was enunciated by the federal government. The goals of the program were to improve the supply, quality, accessibility, and efficiency of collection, processing, storage, and utilization of the nation's blood supply. Among the policies to be implemented were adoption of an all-voluntary blood collection system, resource sharing and regionalization of blood collection and distribution, and initiation of programs to assure appropriate use of blood and blood products.[35] Although no legislation was actually enacted, the announcement of the National Blood Policy became the focal point around which blood banking policy evolved.

The Division of Blood Diseases and Resources (DBDR), created as a division of the National Heart, Lung, and Blood Institute (NHLBI) in the early 1970s, was given the major responsibility at the NIH for

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research and training related to blood and its use. Among the initiatives emanating from the DBDR were actitivies, funded both as grants and contracts, dealing with transfusion-transmitted diseases, immunology related to transfusion practice, and the oxygen-carrying role of blood substitutes. Specialized Centers of Research in Transfusion Medicine were established and the Transfusion Medicine Academic Awards (TMAA) program initiated. The objectives of the TMAA are to develop meaningful curricula using creative educational approaches; to attract students, clinicians, and scientists to the field of transfusion medicine; to cultivate appropriately trained faculty; and to create an environment within the health professions that encourages the maturing of transfusion medicine as a specialty area.[8]

The DBDR has sponsored a number of concensus conferences to help define appropriate criteria for the use of blood and blood products. In addition, the NHLBI and DBDR have initiated a National Blood Resource Education Program (NBREP). The purposes of NBREP are to ensure that there is an adequate, safe supply of blood through motivation of appropriate donors; to educate the public about the safety of the blood supply and the benefits and risks associated with transfusion; and to promote the appropriate utilization of homologous and autologous blood and blood products.

Transfusion Medicine as a Specialty

While the administration of blood has been extensively practiced for over 50 years, it is only in the last decade or so that transfusion medicine has begun to emerge as a recognized discipline. The image of blood service directors as bankers, responsible primarily for overseeing deposits and withdrawals, is fading. Transfusion medicine specialists, be they hematologists or pathologists, are emerging from the bank and becoming increasingly involved in patient care. In addition, many clinicians, especially surgeons and anesthesiologists, are devoting more time to the area of transfusion medicine. Researchers in the basic science disciplines of physiology, biochemistry, immunology, and pharmacology are contributing to the rapidly increasing fund of knowledge related to the appropriate use of blood and blood products in the treatment and prevention of disease.

A comprehensive transfusion medicine curriculum designed to be used in teaching transfusion medicine in medical schools and at the postgraduate level has been published.[24] Compiled by recipients of TMAAs and professional educators, the document is designed to identify the subject areas that are encompassed by transfusion medicine and the knowledge and skills that should be possessed by physicians.

The Use of Component Therapy

The introduction of plastic tubing and bags in the 1950s led to the development of component therapy in the 1960s. Prior to that time, the blood bank supplied two items: whole blood and plasma. The contemporary transfusion service can now provide 25 or more different blood products.[5] Blood is collected into primary bags, which have one, two, or three satellite bags attached with integral tubing. Red blood cells (RBCs), platelets, and plasma have different specific gravities, permitting the components to be separated by differential centrifugation.

Exact data are not available regarding the number of units of whole blood collected or the number of components transfused. Blood donations originally took place in hospital blood banks. However, over 90% of the blood is now collected by blood centers, with the majority of donations taking place in mobile blood units. The regional centers of the American Red Cross collect approximately half of the blood, and centers affiliated with the American Association of Blood Banks (AABB) and the Council of Community Blood Centers (CCBC) collect the rest.[35] There is no coordinated system for sharing data among the three organizations. Similarly, there is no mechanism for collecting data regarding the number of transfusions administered. One estimate is that approximately 14 million units of whole blood are collected each year in the United States and that 2 to 2.5 therapeutic units are derived from each donation.[32] Recent estimates from the American Red Cross are that 20 million component units are transfused to 3.7 million patients annually and that each transfusion averages 5.4 component units.[11]

Reliance on component therapy has led to more efficient use of the blood supply. Without fractionation, specific components would not be available when needed. In addition, administration of components not required by patients is avoided. Because the storage requirements of components differ, separation permits each to be stored at optimal temperature to ensure maximum therapeutic benefit.

There has been a resurgence of interest in the use of fresh whole blood, especially in cardiac surgery patients. One group of investigators has reported that the effect of 1 U of fresh whole blood on platelet aggregation following cardiopulmonary bypass was at least equal, if not superior, to the effect of 8 to 10 U of platelets.[17] The study population consisted of 24 patients who received either 1 U of whole blood or 10 U of platelets. Another group of investigators[37] administered either 2 U of fresh whole blood or 2 U of stored blood to 237 patients following coronary artery bypass grafting. They demonstrated no difference in transfusion requirements, postoperative blood loss, or hemostatic parameters between the groups.

Identification of fatal graft-versus-host disease in several immunocompetent patients who received fresh whole blood has tempered enthusiasm for the use of this product.[15, 33] While irradiation of donor blood may solve this problem by inactivating lymphocytes responsible for graft-versus-host disease, it is unlikely that the use of fresh whole blood will gain popularity because of the logistics of collection and testing, and the lack of proven benefit.

The shelf life of RBCs can now be extended to 42 days if additive solutions are employed. These solutions contain saline, adenine, glucose, and mannitol. In addition to prolonging RBC viability, use of the solutions lowers viscosity and obviates the need for additional saline to facilitate rapid flow during administration. Since outdate rates at most institutions fall below 5%,[9] it is unlikely that efforts will be devoted to further extending the shelf life of RBCs stored in the liquid state. Stored RBC 2,3-diphosphoglycerate can be regenerated by the addition of so-called rejuvenating solutions. RBCs rejuvenated at the end of the permissible storage period can be kept frozen for at least 10 years, probably indefinitely.[9] Whether this technology will be employed, especially in the civilian sector, remains to be seen.

The introduction of new plasticizers in the early 1980s made possible the extension of the shelf life of platelets to 5 days. The plastic containers currently in use allow better oxygen and carbon dioxide exchange through the walls of the container, thereby delaying the accumulation of metabolic byproducts. Platelets are stored at room temperature for optimal post-transfusion function. Storage beyond 5 days is currently limited by the risk of bacterial growth. In contrast to red blood cells, the outdating of platelets is a significant problem, often approaching 10% or more of the inventory.[9] Elucidation of the cold-induced storage lesion would permit refrigerated storage of platelets, thereby decreasing the potential for bacterial growth and extending the shelf life.

The development of hemapheresis equipment in the last two decades has made possible the selective collection of one or more blood components. The demand for single-donor platelets collected by automated hemapheresis has increased dramatically. A significant percentage of patients who receive repeated platelet transfusions become alloimmunized and refractory to random-donor platelets. The majority of such patients respond to donors selected on the basis of HLA match. The use of single-donor platelets also decreases the number of donor exposures. However, the trend toward increased use of single-donor platelets is limited by the availability of donors, the time and expense associated with the procedure, and concerns for donor safety.

Blood cell separators are also used for collecting white blood cells for transfusion. Granulocytes are used to treat neonatal sepsis and infection in patients with inherited defects of granulocyte function, but reports of the efficacy of such therapy are largely anecdotal. There are even less data regarding granulocyte therapy in granulocytopenic patients with bacterial or fungal sepsis. Unless controlled studies demonstrate the efficacy of prophylactic or therapeutic granulocyte therapy, there will be no trend toward its use.

The Safety of the Blood Supply

Recognition in the early 1980s that the human immunodeficiency virus (HIV) could be transmitted via blood transfusion[12] markedly influenced transfusion practices as well as donor screening procedures. Voluntary exclusion of persons at high risk of AIDS was introduced early in 1983, and a system to allow donors to indicate confidentially that their donated blood should not be used for transfusion was instituted in 1986. Testing for antibody to HIV was initiated in the spring of 1985.

Most recent estimates are that between 14,000 and 15,000 cases of AIDS will eventually occur in patients between 13 and 69 years of age who were transfused prior to July 1985.[16] Estimates for the risk of contracting HIV infection during 1987 were 1:153,000 per unit transfused. For the patient who received the average transfusion of 5.4 U, the odds were 1:28,000. The number of units of blood infected with undetected HIV that were transfused in 1987 was estimated at 131 (range, 67 to 227).[11]

Although fear of transmission of HIV has influenced transfusion trends to a greater extent than concerns about post-transfusion hepatitis, the latter has been a recognized complication of transfusion for a much longer period of time. In the late 1960s, up to a third of multiply transfused patients developed icteric or nonicteric hepatitis.[9] The virtual elimination of paid donors in the 1970s led to a substantial reduction in the incidence of hepatitis. However, the introduction of testing for hepatitis B surface antigen (HBsAg) in 1972 is estimated to have accounted for no more than a 25% reduction in the incidence of post-transfusion hepatitis[1] because most cases are non-A, non-B hepatitis (NANBH). Studies conducted prior to 1980 indicated that the incidence of post-transfusion hepatitis was 7% to 12%.[2] The current incidence is unknown, but it is believed to be significantly lower as a result of more rigorous donor screening and the introduction of additional testing procedures. Recent Centers for Disease Control estimates suggest that the number of persons who develop post-transfusion NANBH annually is 7500 to 15,000.[3] Surrogate testing is credited with exclusion of approximately 50% of potential donors infected with the NANBH virus. The recently reported cloning of the NANBH agent, now designated as hepatitis C virus (HCV), has led to the development of both radioimmune and enzyme-linked assays for antibody detection.[2] Anti-HCV screening was initiated in May 1990.

While the blood supply is undoubtedly safer than ever before, the general public, patients, and physicians are still concerned. Results of a nationwide public opinion survey conducted on behalf of the AABB in 1989 (AABB Newsbriefs, vol 12, August 1989) indicated that Americans' concerns about contracting AIDS from donating or receiving blood continued to lessen in the years since the first survey was conducted in 1985. Nevertheless, 20% of respondents still believe that AIDS can be contracted from blood donation. Fifty-two percent believe that it is unlikely that recipients of tranfusion will contract AIDS. When queried about major concerns if they faced surgery, 27% cited complications from errors made by doctors and medical staff as their major concern. Seventeen percent cited the possibility of contracting AIDS from transfusion, while 16% mentioned complications from anesthesia. It can be assumed that concerns about transfusion-transmitted disease will continue to influence trends in transfusion practices.

BLOOD UTILIZATION

Transfusions of blood and blood components in the United States doubled between 1971 and 1980. However, the results of a recently reported survey of transfusion activities during the 1980s indicate that transfusion rates are not continuing to follow the trend of the 1970s.[31]

Annual transfusion activity between 1980 and 1985 was surveyed in four sets of hospitals, which together accounted for approximately 5% of the red blood cell transfusions in the United States in 1980. A total of 103 hospitals (29,092 beds) were included in the study. Hospital admissions during 1980 were 970,063, and the number of RBC units transfused was 484,226, or 499 U per 1000 admissions. The regions of the country and the hospitals surveyed represented a select group with demonstrated interest in the area of transfusion medicine. Group A included nine university-affiliated teaching hospitals in Massachusetts, seven of which were located in Boston. Group B consisted of 14 university-affiliated teaching hospitals in 11 states. Each of the hospitals had a faculty member who was a recipient of a TMAA from the NHLBI. The size and location of the hospitals were divergent, and none was located in a metropolitan area with a high number of AIDS cases. Group C included 38 hospitals in the Puget Sound region of Washington served by the Puget Sound Regional Blood Program and Center. The 42 hospitals in the San Francisco area served by the Irwin Memorial Blood Bank of the San Francisco Medical Society made up group D. With allowance for the fact that the data represent a rather unique group of institutions, the information can be viewed as indicative of trends in transfusion in the United States.

RBC transfusions increased significantly between 1980 and 1982 in all groups of hospitals. The range was 5.7% in group A to 18.6% in group C. Patterns differed, however, after 1982. In group A (Massachusetts) and group D (San Francisco), the rates of RBC transfusion declined. The transfusion rate in group D in 1985 was 10.4% below the 1982 rate. In contrast, the transfusion rate increased by 2.9% in group B (TMAA hospitals) and 0.9% in group C (Puget Sound).

Transfusions of plasma followed a similar pattern. Plasma transfusion rates increased in all hospital sets between 1980 and 1982. The overall increase was 15.8% and the range, 5.2% to 44.4%. In three of the four sets, the growth subsided in subsequent years. Interestingly, transfusions of plasma in the Puget Sound area doubled during this time. However, the dependence of hospitals in this area upon plasma transfusion was low throughout the entire period.

The most striking change was the increase in platelet transfusions throughout the period. In each set of hospitals, the 1985 rate of platelet transfusion was more than 50% above the 1980 rate. The overall increase was 30.5% between 1980 and 1982 and 34.9% between 1982 and 1985.

Autologous transfusions were also surveyed. The rate of predeposit of autologous blood by surgical patients was very low at the beginning of the study period. It increased in all areas. However, the rate of increase in group D (San Francisco) was most impressive; at the end of the study period, the number of autologous units represented 3.5% of RBC transfusions.

The researchers attributed the changes in RBC and plasma transfusion practices to concerns of patients and physicians about the risk of acquiring AIDS through transfusion. They suggested that the difference in platelet transfusion dynamics was a consequence of the more serious clinical status of platelet recipients and the smaller number of patients. They point out that patients are usually transfused with large numbers of platelet units, whereas the average transfusion of RBCs or plasma is less per patient.

The author of the accompanying editorial suggested that other factors might also have played a role in the trends identified.[22] The impact of cost containment was not addressed. Intraoperative and postoperative blood salvage techniques became more widely used during the study period. The Joint Council on the Administration of Healthcare Organizations (JCAHO) placed more stringent requirements on the auditing of transfusion practices, which may have led to decreased use of blood components. Finally, the changes in medical and surgical therapies during the period of study must be taken into account.

Advances in surgical techniques and medical therapies determine, to a great extent, the demands placed upon the blood supply. The 1970s saw the rapid growth of cardiac surgical procedures. In addition to receiving several units of RBCs, most of the patients also received platelets and fresh frozen plasma prophylactically. Several factors led to a lowering of the number of homologous blood exposures for cardiac surgery patients in the 1980s. It became common to accept lower hematocrits in the postoperative period.[10] The use of prophylactic fresh frozen plasma and platelets[25] was no longer routine in many centers. Most importantly, the use of autologous transfusion increased significantly. Preoperative blood donation and intraoperative and postoperative blood salvage are now commonplace procedures.

The surgical procedure of the 1980s that had the greatest impact on the blood supply in some regions of the country was liver transplantation. Blood use during the first 5 years (1981–1985) of the liver transplant program in Pittsburgh has been extensively reviewed.[19] The mean RBC use in 366 adult transplants was 25 U. Over the course of the 5 years, the mean use decreased from 36 to 17 U. Platelet use remained constant at about 20 U/case. While patients admitted for liver transplantation represented less than 0.01% of the 31,000 patient admissions at the two hospitals performing liver transplants in Pittsburgh in 1985, they used about 25% of the blood products. RBC use by liver transplant patients accounted for 3% of the RBCs issued by the Central Blood Bank of Pittsburgh, 9.2% of fresh frozen plasma, 8.6% of the platelets, and 7.1% of the cryoprecipitate.

Table 1. *Responses to American Society of Anesthesiologists Survey of Transfusion Practices*

QUESTION	AFFIRMATIVE RESPONSE (%) 1981	1988
Do you require patients undergoing elective surgery to have a hemoglobin level of at least 10 g/dL?	65	35
Is there a mechanism established in your primary hospital for patients to predonate blood for elective surgery?	49	92
Do you ever employ isovolemic hemodilution (e.g., withdraw blood immediately prior to surgery and reinfuse it later in the procedure)?	22	31
Do you ever use any type of apparatus for intraoperative salvage and reinfusion of blood?	39	77

TRANSFUSION PRACTICES

In 1981, the American Society of Anesthesiologists (ASA) conducted a survey of transfusion practices among a randomly selected group of active members.[29] The survey was repeated in 1988. Data from the surveys are included in Table 1. Two trends are apparent: an arbitrary preoperative hemoglobin level is required less often and the use of autologous transfusion has increased.

Participants were also asked to list what they considered to be the major problems in transfusion practices. The most frequent response in 1981 was lack of available blood products. Concerns about excessive transfusions, lack of education regarding component therapy, the time required for processing of transfusion requests, clerical errors, and nonavailability of transfusion devices were cited by a smaller number of respondents. Excessive crossmatching; lack of cooperation among anesthesiologists, surgeons, and blood bank personnel; the cost of blood products; methods of estimating blood loss; and blood conservation were also mentioned. In 1988, 41% of respondents listed fear of transfusion-transmitted disease as their primary concern. Difficulty in obtaining whole blood, the lack of data regarding appropriate indications for blood components (especially fresh frozen plasma) administration, and inadequate use of transfusion experts in determining appropriate blood use were cited by a minority of respondents.

When asked if a maximum surgical blood ordering schedule (MSBOS) was used, 24% of respondents replied affirmatively in 1981 and only 30% in 1988. Thirty percent replied each time that none was available. The percentage who answered "do not know" in 1981 was 40% and in 1988, 46%. Since the advantages of such systems in reducing unnecessary crossmatching and excess inventory of RBCs while not compromising the safety of transfusion have been demonstrated, the responses are somewhat surprising. One is tempted to speculate that the "do not know" answers should have been "yes."

In 1981, 37% of respondents stated that they used microaggregate filters for all transfusions. Surprisingly, the percentage was virtually identical (38%) in 1988. Several publications, including the booklet entitled "Questions and Answers about Transfusion Practices," published by the ASA (American Society of Anesthesiologists, 515 Busse Hwy, Park Ridge, IL) and distributed to all members in 1987, clearly stated that there is no indication for the routine use of microaggregate filters, even when large volumes of blood are administered. The filters are useful in preventing febrile transfusion reactions in repeatedly transfused patients.[27] The place of newly introduced filters that remove white blood cells has yet to be determined.[26] However, one can speculate that the use of these very expensive filters will become popular in the absence of proven indication.

A common practice of the 1970s that was not addressed in the survey was the administration of calcium and sodium bicarbonate on an empiric basis to patients who received multiple RBC transfusions. While firm data are not available, clinical observations indicate that this practice is no longer prevalent.

The use of various types of autologous transfusion has increased in the last few years. Preoperative donation, a practice that was formerly significantly underutilized,[34] is now being offered to more patients. Intraoperative salvage and reinfusion of shed blood is becoming routine in many operating rooms, especially for spine surgery, joint replacements, and cardiovascular procedures. Postoperative salvage is used in many centers following cardiac surgery. The place of postoperative salvage in other procedures has yet to be determined. Intraoperative hemodilution is not commonly employed. Because some states, notably Texas and California, have enacted legislation requiring that the alternatives to homologous transfusion, as well as the risks and benefits, be explained to patients, it may be anticipated that the use of autologous transfusion will become a standard of care for many operative procedures.

The question of informed consent for transfusion is not resolved. Recognizing the importance of the issue, the AABB sponsored a conference devoted to the topic in 1989.[38] Ideally, the risks, benefits, and alternatives to homologous transfusion should be discussed with surgical patients at the time the proposed surgery is discussed. The night before the operation, when alternatives such as predonation are no longer an option, is too late. Some hospitals require that a consent form be signed. Alternatively, a note can be placed in the patient's chart indicating that the potential need for transfusion was discussed and that the patient's questions were answered.

Evaluating the appropriateness of blood transfusion, an important function of transfusion committees, is required by the JCAHO.[21] All too often the transfusing physician is asked long after the patient's discharge to justify a transfusion episode. The trend in auditing practices is toward concurrent and prospective auditing.[23] With concurrent audits, blood component orders are reviewed soon, usually less than 24 hours, after the transfusion. An even more effective practice, albeit more demanding of personnel, is the prospective audit. With this method, blood requests are reviewed prior to release of the blood by the transfusion service. This process has the potential for alteration of intended transfusion therapy.

Two studied addressing the appropriateness of transfusions have recently been published. The overall incidence of transfusion episodes judged inappropriate by predetermined criteria was 26% in one study[30] and 42% in the other.[18] Both groups of investigators found that fresh frozen plasma was the component administered inappropriately most frequently (69% and 83%). One of the groups[30] studied transfusion practices over a 3-year period. They found a trend toward more appropriate transfusions, but the overall rate of inappropriate transfusion episodes was 22%.

TRANSFUSION TRENDS IN THE FUTURE

The trend toward more conservative transfusion practices will continue. Hopefully, research in the area of oxygen transport, coupled with the development of noninvasive methods of monitoring oxygen delivery and consumption, will make possible therapeutic decisions that are based on science, not habit. The search continues for a RBC substitute. Chemically modified acellular hemoglobin or recombinant hemoglobin may be available for use within a few years. Its role remains to be defined.

Autologous transfusion will continue to increase. Administration of recombinant erythropoietin may become an adjunct to preoperative autologous donor programs. Preliminary studies have shown that the number of units that can be donated in the preoperative period is greater when erythropoietin is administered.[13] New approaches to instrumentation as well as modifications of existing devices for intraoperative and postoperative salvage of shed blood should assure the continued growth of this form of autologous transfusion. Hemodilution, not extensively employed at this time, will probably be used more frequently as information becomes available regarding appropriate applications, limitations, and contraindications to use of the technique.

While the benefits of directed donor[28] and limited-exposure donor programs[7] have yet to be determined, it can be anticipated that such programs will increase. Commercial ventures into the storage of blood for autologous or designated homologous use in the absence of foreseeable medical need have not proved to be the financial success that was envisioned. Growth in this area is not anticipated.

The place of pharmacologic approaches to reducing blood loss, such as the administration of desmopressin or aprotinin, is not yet clear. The results of currently available studies using desmopressin are not consistent[14, 20]; however, preliminary reports of the use of aprotinin are quite promising.[4, 36] Even if this modality does prove beneficial, the overall impact on blood use should not be great.

There is no doubt that the safety of the blood supply will continue to be of paramount importance to the public, patients, and physicians. If new tests capable of detecting the presence of infectious agents that might, even rarely, be associated with transfusion-transmitted disease are developed, they will be added to existing tests of donor blood. Research in the area of inactivation or removal of microbial agents potentially present in donor blood continues.[9]

A growing body of knowledge attests to the fact that blood transfusion affects the immune system.[6] There is an apparent association between transfusion and an increased risk of cancer recurrence. In addition, transfusion may impair host defenses against bacterial infection. Although the mechanism remains unclear, concerns about the immunomodulatory effects of transfusion are a factor in the trend toward more conservative transfusion practices that is expected to continue.

SUMMARY

Trends in transfusion practices reflect developments in other areas of medicine. Advances in surgical techniques made possible open heart surgery and liver transplantation, which markedly increased the demand for blood. The widespread use of cancer chemotherapy also increased the need for blood products. Recognition that HIV could be transmitted through transfusion was the most potent stimulus for limiting homologous transfusion and promoting autologous transfusion. Technologic advances made possible component therapy, salvage and reinfusion of shed blood, and hemapheresis. While it is reasonable to assume that the current trends in transfusion practices will continue, new discoveries in medical science could potentially dramatically alter these practices.

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Autologous Transfusion

*Pearl Toy, MD**

Autologous transfusion is the collection and reinfusion of the patient's own blood or blood components. The three forms of autologous transfusion are preoperative autologous blood donation (PABD), perioperative blood salvage, and acute normovolemic hemodilution. Most planned surgical procedures do not result in enough blood loss to require transfusion; autologous blood strategies are not necessary for most elective surgery patients. However, autologous blood is the transfusion of choice for appropriately selected surgical patients undergoing procedures that result in enough blood loss to require transfusion.[17, 63] Together with meticulous surgical hemostasis, homologous transfusions can be minimized.[42]

HISTORY

Autologous transfusion was available and advocated[2, 7, 16, 39, 52] but rarely used except in Jehovah Witnesses[14] before 1980, because bank (homologous) blood was considered safe. In the 1980s, fear of transfusion-transmitted human immunodeficiency virus (HIV) greatly increased interest in the use of autologous blood.[12, 17, 26, 28, 33, 49, 57, 62, 68] In early 1986, PABD was still underused.[61] In 1987, the American Association of Blood Banks established a National Autologous Blood Resource Center to provide information and assistance. In 1988, the National Institutes of Health established an Expert Panel to address issues concerning autologous transfusion.[63] On hindsight, the best period to use autologous transfusion was between 1978 and 1985, when no specific tests were available to detect HIV or hepatitis C in donor blood. In mid-1985, blood banks began testing donor blood for antibodies to HIV, and in 1990, blood banks began to test donor blood for antibodies to hepatitis C.

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COST-BENEFIT

The medical benefits of autologous transfusion include avoidance of transfusion reactions and transfusion-associated diseases. These benefits are difficult to estimate in dollars, especially with the changing rates of transfusion-associated infections. The immediate savings, however, are associated with reduced use of homologous blood, and these savings may offset the cost of autologous transfusion. A unit of autologous blood generally costs more than a unit of homologous blood because it takes more personnel time to collect blood from a patient who often has not donated before. The cost of perioperative salvage includes equipment, personnel operator time, and disposable software costs. The greater the number of units salvaged, the greater the savings in homologous blood costs.[54]

In liver transplantation, Williamson found intraoperative salvage costs were 23% higher than homologous blood.[64] In vascular surgery, Tawes et al[58] found that software costs were covered when two or more units of packed red cells were salvaged. In coronary artery surgery, Hiratzka et al[24] found the cost fell 23% per patient with use of the cell saver. In aortic surgery, Cutler[13] found the cell saver to be cost-effective. Due to the different methods of cost accounting used in the above-mentioned studies, it is not absolutely clear that autologous transfusions are always immediately cost-effective. Without knowing the risk, morbidity, and mortality of transfusion-associated infections, particularly hepatitis C, the total financial benefit is unclear.

PREOPERATIVE AUTOLOGOUS BLOOD DONATION

Selection of Patients

The ideal patient for PABD is one who has 2 or more weeks before surgery, is likely to need a blood transfusion during or after surgery, and has a hemoglobin level of 11 g/dL (hematocrit, 33%) or greater.[55, 63] Patients undergoing total hip replacement or scoliosis repair are often ideal candidates.[59, 65] Elderly patients, even those who have never donated before, can successfully undergo PABD[23, 46] and actually have lower donor reaction rates.[40] Persons weighing less than 110 lb can donate volumes reduced in proportion to their body weight, and children as young as 8 years old have successfully donated.[43, 53] Among pregnant women, those with placenta previa should donate as soon as the diagnosis is made,[29, 41] but PABD should not be routinely encouraged for normal pregnant women. Patients undergoing cardiac or vascular surgery can safely donate[35, 37, 45] if there is no significant risk in delaying surgery for PABD. Although increasing angina occurs in a few patients who donate,[6] it is unclear whether this merely represents natural progression of disease or whether donation actually increases angina. The risk of blood donation may be higher for patients with unstable angina or severe aortic stenosis, and these patients are usually not candidates for PABD.

Procedure

The optimal donation period begins 4 to 6 weeks prior to surgery, and the last blood donation is usually collected no later than 72 hours before surgery to allow for blood volume restoration.[1, 55] The patient should take a therapeutic dose of oral iron and typically donates once a week. Recombinant erythropoietin increases the number of units collected by 1 unit.[19] Patients who donate a unit several days preoperatively benefit little because red blood cell (RBC) regeneration is limited unless erythropoiesis has been stimulated (about 1.5 times) by weekly donation.[9, 27]

Risks

The risks of PABD include vasovagal reactions and progression of underlying disease due to surgical delay.[63] Approximately 3% of autologous or homologous blood donations are associated with lightheadedness, 0.3% with transient loss of consciousness, and 0.03% with self-limited seizures.[34, 40, 50] Persons more likely to react are those who have had previous reactions, first-time donors, women, and persons of low body weight.[40] A vasovagal reaction manifested by hypotension and bradycardia may carry the risk of higher morbidity for patients with cardiac or cerebrovascular disease, but this has not yet been demonstrated.

Testing of Autologous Blood

In accordance with the Food and Drug Administration's (FDA's) recommendations, all blood, homologous and autologous, should be tested for ABO group, Rh type, hepatitis B surface antigen (HBsAg), anti-HIV, syphilis, and anti-HTLV-1. If a unit is confirmed to be anti-HIV or HBsAg positive, the FDA recommends that it not be used. However, such units can be given back to the patient provided a written, signed, and dated request is received from the patient's physician. An exception to HBsAg and anti-HIV testing can be made, if the autologous blood is collected and transfused in the same hospital, according to American Association of Blood Banks standards.[55]

Transfusion of Autologous Blood

There are still some small risks associated with the transfusion of autologous blood, due to improper storage or administration. Therefore, autologous blood should not always be reinfused just because it is available. Clinical assessment of risk and benefit should be made as with all transfusions.[36, 44, 51]

Release of Blood into the General Pool

Autologous units are usually reserved for the donor-patient until the patient's discharge or the unit's outdate, depending on local policy. If a second surgical procedure is anticipated, the transfusion service should be requested to extend storage and rejuvenate the RBCs if necessary. Whether unused autologous units should be released into the general pool is controversial, and practice varies.[3] Inadvertent premature release results in autologous blood not being available for the donor at a later date. Conflicting evidence exists as to whether autologous units are as safe as regular homologous units, despite the fact that autologous donors are screened and tested.[20, 30, 48] The main advantage of releasing unused autologous blood to the general supply is not to waste good blood. However, such units are thought to contribute little to the overall supply and should not be considered a justification for ordering autologous donations from patients who are not likely to require transfusion.[63]

PERIOPERATIVE BLOOD SALVAGE

Surgical patients likely to need transfusion can benefit from perioperative blood salvage, either intraoperative[47] or postoperative, especially in cases where PABD is impossible or inadequate. The only two situations where blood lost during an operation should not be reinfused are when the operative field may be contaminated with bacteria or malignant cells. Blood salvaged perioperatively should not be transfused back to the patient or discarded within 6 hours of initiation of the collection.[55]

Intraoperative Blood Salvage

Intraoperative blood salvage is useful in cardiac,[4, 11, 18, 60] vascular,[11, 13, 22, 58] and orthopedic[5, 32] surgical procedures; liver transplantations[15, 64]; and some trauma cases.[67] Blood salvaged intraoperatively may be transfused directly after collection or washed prior to infusion. Unwashed blood can be suctioned and reinfused using a blood filter, using canister systems, which are inexpensive and easy to use. The limitation of such systems is that they may not be rapid enough for massive blood loss. The potential concerns of unknown clinical significance include the infusion of free-hemoglobin and tissue procoagulants found in unwashed blood.

Blood can be suctioned from the operative field, washed in a cell washer, and returned as packed RBCs. Current models, frequently performed by cardiac perfusionists, can process a unit of salvaged blood in a few minutes.

Postoperative Blood Salvage

Following cardiac surgery[25] or trauma, blood collected from chest drains can be transfused without washing. Because blood in the pleural and abdominal cavities is defibrinated, it does not require anticoagulation prior to transfusion.

Risks of Perioperative Blood Salvage

The potential risks of reinfusion of unwashed blood are disseminated intravascular coagulation due to transfusion of tissue procoagulants and renal insufficiency due to transfusion of hemolyzed cells.

While these are potential risks, laboratory abnormalities, but not clinical effects, have been observed.

The risks of reinfusion of washed blood are dilutional coagulopathy and reinfusion of anticoagulants. Washed blood is deficient in coagulation factors and platelets and is therefore equivalent to washed RBC units. In the operating room, the anesthesiologist must keep track of the total number of RBCs transfused from the cell saver and from regular packed RBCs. After one or two blood volume (10 to 20 U) replacements with RBCs, dilutional thrombocytopenia and coagulopathy may occur. When heparin is used as the anticoagulant in the cell saver, equipment malfunction may cause systemic anticoagulation.

ACUTE NORMOVOLEMIC HEMODILUTION

Acute normovolemic hemodilution involves the rapid phlebotomy of the patient's blood and its simultaneous replacement with crystalloid or colloid immediately before a surgical procedure.[38] This procedure has been used in cardiac[8] and other surgery. This would dilute the intraoperative hematocrit and decrease the absolute RBC mass lost during the operation. For example, if whole blood lost during surgery is 1000 mL and the hematocrit is 45%, the RBC loss is 450 mL; if the hematocrit is 25% after hemodilution, then the RBC loss is only 250 mL, and 200 mL (1 U) of RBCs are saved. From this calculation, it can be seen that this procedure results in significant savings of RBCs only if intraoperative bleeding exceeds a liter and the hematocrit is diluted to the low twenties. This usually requires phlebotomy of 40% of the blood volume, i.e., 1500 to 2000 mL of whole blood in an adult.

The procedure for acute normovolemic hemodilution has been described.[31, 56] Briefly, an artery or a central or large peripheral vein is chosen for phlebotomy. Following induction of anesthesia, but prior to surgical incision, the needle is placed in a sterile manner and 3 to 4 U of blood are removed. The blood is drawn into blood bags containing anticoagulant and is labeled with the patient's name, hospital number, time of phlebotomy, and clearly marked "For autologous use only." For each milliliter of blood removed, 2 to 3 mL of crystalloid are infused to retain intravascular volume. Alternatively, each milliliter of blood removed is replaced by 1 mL of colloid solution. The blood is kept in the operating room with the patient and maintained at room temperature for 6 hours or less. After 6 hours, blood must be refrigerated, in a monitored refrigerator, and must be transfused within 24 hours.[55] The hematocrit should be determined following phlebotomy and at intervals during surgery and after transfusion. An appropriate inspired oxygen concentration must be administered to ensure adequate tissue oxygenation. After the period of major blood loss has ceased, the patient's own blood is reinfused.

While healthy young patients can tolerate an intraoperative hematocrit of 25% or less, the safe lower limit of the posthemodilution hematocrit is unknown in the more typical middle-aged or elderly elective surgery patient. Abnormal bleeding due to dilution of platelets and coagulation factors does not occur, because a decrease in the levels of these factors does not reach levels in the range usually associated with clinical bleeding.[31]

DIRECTED DONATIONS

Directed donors are persons chosen by the patient, and the directed donation is intended for the specific patient-recipient. This option is mandated by some states and not in others. Directed donations actually may be less safe than volunteer donations.[10, 66] Logistic and administrative problems increase cost and the chance of errors.[10] Directed donor blood from siblings, parents, or children of the recipient are currently irradiated to prevent graft-versus-host disease in the recipient.

SUMMARY

Autologous transfusion decreases or eliminates the risks associated with homologous transfusion and should be used for eligible patients likely to require a transfusion. One or more of the following techniques can be used. Preoperative autologous blood donation is ideal for patients who have 2 or more weeks before surgery, are likely to need perioperative transfusion, and have a hemoglobin level of more than 11 g/dL. Large intraoperative blood losses can be salvaged and reinfused if the operative field is not contaminated with bacteria or tumor cells. Similarly, postoperative blood in mediastinal and chest drains can be reinfused. If the patient can tolerate hemoglobin concentrations well below 10 g/dL intraoperatively, acute normovolemic hemodilution may be considered. In combination with excellent surgical hemostasis, autologous transfusion techniques can minimize homologous transfusions in some surgical patients.

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Acute Intraoperative Hemodilution and Perioperative Blood Salvage

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Landmarks of the first 80 years of blood transfusion include the demonstration of blood groups by Karl Landsteiner and the development of immunologic techniques for cross matching; the evolution of the technology of component preparation and preservation, which has enabled greater blood banking efficiency and tailoring the transfused products to a specific patient's requirements; and finally, the increased utilization of blood conservation and modalities of autologous blood transfusion. Blood conservation and the utilization of autologous blood transfusion have been fostered by increasing demand for blood and components, combined with increasing recognition of the complications of blood transfusion, including disease transmission. The complications of homologous blood and component transfusion include the transmission of viral hepatitis and retrovirus, principally acquired immunodeficiency syndrome (AIDS)-associated human immunodeficiency virus-1 (HIV-1) and related viruses,[8, 41, 53] alloimmunization, acute pulmonary reactions, and graft-versus-host disease.[70] Further, increasing evidence that perioperative homologous blood transfusions decrease the time to recurrence and the survival from colorectal cancer[67] and other cancers has compelled surgeons to review their blood and component transfusion policies.[4, 26] Public fears have been heightened primarily by concern for the transmission of the AIDS virus by blood and blood products, and an informed public now recognizes that there are alternatives to blood bank supplies, which includes reinfusion of their own blood.[1, 69]

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Autologous blood transfusion comprises three technologies: (1) predeposit for patients whose elective surgery is scheduled far enough in advance to permit collection and storage of blood; (2) intraoperative removal of blood and replacement with crystalloid and/or colloid to achieve acute normovolemic hemodilution (ANH) and subsequent reinfusion of the fresh autologous blood; and (3) perioperative salvage of blood and the administration of either processed (washed) red blood cells (RBCs) or unprocessed blood during or after surgery.

The goals of this article are to review the techniques, role, safety, and efficacy of autologous blood transfusion associated with acute intraoperative hemodilution and perioperative salvage and the associated physiologic and biochemical changes. However, effective blood conservation strategies often involve predeposit programs, which have an impact on the role and efficacy of hemodilution and perioperative salvage.

HISTORICAL PERSPECTIVE

History generally credits Richard Lower, who demonstrated transfusion before distinguished scientists in Oxford, England, with the first blood transfusion in 1666 in animals. The publication the following year in the *Philosophical Transactions of the Royal Society* made the technique available to European physicians.[74] Although several physicians transfused animal blood to humans in the mid-seventeenth century, further development of transfusion was prevented by the Faculty of Medicine of Paris and the French Parliament (1668) following the death of a recipient. No advance was made in blood transfusion until the early nineteenth century, when an English obstetrician, James Blundell, observing the helplessness of women with postpartum hemorrhage, reinvestigated blood transfusion. Not only did he have some successes with homologous blood transfusion,[5] he is also credited with the first recorded transfusion of salvaged blood.[76] More than a century later many of the major problems that plagued homologous blood transfusion were to yield to scientific research and organizational progress. Thus, the success of homologous blood transfusion and the organization of blood transfusion services reduced the need for and interest in autologous blood transfusion.

Blood Cell Salvage With Autologous Transfusion

For more than a century following Blundell's reports on blood salvage and transfusion there were only sporadic reports of blood salvage.[28, 76] In most cases, the blood loss was massive, and despite the low complication rate, general acceptance was absent. Autotransfusion was most frequently reported in obstetrics and gynecologic surgery (e.g., ectopic pregnancy), and by 1931, there were 282 reports in the literature of blood salvage and autotransfusion with many subsequent cases, as described by Wilson and Taswell.[76] The overall mortality rate (2.2%) was lower than the rates in clinically similar large series and included patients with severe blood loss.

Davis and Cushing[17] reported the successful use of autologous blood transfusion in 23 patients undergoing major neurosurgery at Peter Bent Bringham in 1925. The cases included vascular meningiomas as well as intracranial tumors. Intraoperative salvage with autologous blood transfusion has also been reported extensively in trauma, including battle casualties. Indeed, Wilson and Taswell consider there is evidence that autologous blood transfusion was used by British surgeons in India in 1865 and by the Germans in World War I.[76] Griswold and Ortner,[23] in 1943, reported on 100 cases of thoracic or abdominal trauma in which autologous blood transfusion was used. The mortality rate (30%) was less than would be expected from the magnitude of trauma.

Hemodilution With Autologous Blood Transfusion

The concept of intraoperative removal of blood and replacement with crystalloid or colloid for patients undergoing cardiac surgery utilizing cardiopulmonary bypass or hypothermic circulatory arrest was reported by Laver et al.[42, 43] Initially, hemodilution in cardiac surgery utilizing cardiopulmonary bypass was achieved by using a cell-free prime. Laver and associates and others also reported hemodilution after induction of anesthesia but before surgery by withdrawing up to 20% of the patient's blood volume and subsequently returning this fresh autologous blood to the patient after bypass. In addition to hemodilution as a prerequisite to minimize the increased viscosity associated with hypothermia, the reinfusion of the freshly harvested blood was thought to mitigate postbypass bleeding. Therefore, hemodilution with subsequent transfusion of the autologous blood gained acceptance in the management of both cardiac and noncardiac surgery in Jehovah's Witness patients, in whom hemodilution procedures were acceptable. It was also utilized in cardiac surgery to reduce the viscosity associated with hypothermia, to minimize postbypass bleeding, thereby reducing homologous blood and component transfusion,[25, 42, 43] and where compatible homologous blood was not available.

HEMODILUTION

Acute intraoperative normovolemic hemodilution is defined as the reduction of the hematocrit or hemoglobin concentration by the withdrawal of blood and the simultaneous volume replacement with cell-free substitutes. The harvested whole blood is stored at room temperature and reinfused within 4 to 6 hours after the major surgical blood loss has been controlled. Sufficient blood is withdrawn from a central venous or aterial catheter to reduce the hematocrit to a target value, usually from 25 to 30 vol% (mild) to 20 to 24 vol% (moderate hemodilution). Hemodilution to a hematocrit less than 20% in the absence of hypothermia and cardiopulmonary bypass is considered to be associated with impaired oxygen delivery.[61] The ratio of cell-free substitute to blood withdrawn has ranged from 1:1 to 4:1, with higher ratios associated with crystalloid replacement. Therefore, in order to optimize hemodynamic function and oxygen transport, the intravascular volume is increased at the time of hemodilution and is often maintained at a high volume to compensate for extravascular loss during surgery. Although the term *acute normovolemic hemodilution* has most frequently been used in the literature, perhaps *euvolemic* or even *hypervolemic hemodilution* would be more accurate. For simplicity in this review, the term *acute normovolemic hemodilution* will be used. The colloids used include 5% albumin, dextran, and hetastarch. Some of these colloids may also decrease viscosity as well as alter blood coagulation profiles. Therefore, interpretation of both experimental and clinical studies of hemodilution is complicated by the magnitude of hemodilution and volume replacement, crystalloid, and, if used, type of colloid, as well as anesthesia and, in clinical studies, the concurrent surgery.

Technique

In both cardiac and noncardiac surgery, ANH is achieved after induction of anesthesia but before or concurrent with the commencement of surgery. The autologous blood volume (ABV) to be withdrawn is calculated from the prehemodilution hematocrit (zero time) (H_o), the target hematocrit (H_T), and estimated blood volume (EBV):

$$\mathrm{ABV} = \frac{\mathrm{EBV} \times (H_o - H_T)}{(H_o + H_T)/2}$$

where $(H_o + H_T)/2$ is the average of the prehemodilution and the target hematocrits.[31] The EBV is calculated using conventional estimates based on lean body weight: body weight > 20 kg, EBV $= 70$ mL/kg; body weight 10 to 20 kg, EBV $= 75$ mL/kg; body weight $<$ 10 kg, EBV $= 80$ mL/kg. It is safer to underestimate the EBV than to overestimate and remove an excess volume. Blood is withdrawn over a period of 30 to 45 minutes consistent with the patient's hemodynamic status and with concurrent administration of crystalloid (e.g., lactated Ringer's solution) or combination with a colloid. The ratio of crystalloid to ABV is usually 2:1 or greater whereas where colloid has been used, the ratio is usually 1:1.[45]

Blood may be withdrawn from an arterial line (e.g., radial), with periodic monitoring of the arterial pressure, or from a central venous line. Several commercial systems are available to collect the withdrawn blood (4R5010 and 4R5012, a two-CPD Blood-Pack with a Y-type collection set; Typenex blood-recipient identification band, Fenwal, Deerfield, IL). The capacity of each collection bag is approximately 450 mL, and the volume of the CPD is 63 mL. During collection the blood bag should be gently rocked to mix the incoming blood with the CPD solution. There are two limitations to these systems:

inaccuracy of volume of blood collected and a decrease in the ratio of blood to anticoagulant when smaller volumes are collected in pediatric patients. Therefore, when the withdrawal and replacement are manual, it is recommended that the collecting bags be weighed before and frequently throughout collection and that the hematocrit or hemoglobin level should be measured prior to hemodilution, halfway through, and at the completion of blood withdrawal.

Miller and associates[52] examined the safety and efficacy of controlled withdrawal of blood with graded mixing of anticoagulant with harvested blood and the simultaneous infusion of lactated Ringer's solution using pumps of Cobe 2997 Cell Separator (Cobe, Lakewood, CO). The centrifuge was bypassed. In a prospective study series of patients undergoing reconstructive surgery for scoliosis, Kafer and associates[34] demonstrated that this method permitted a high level of accuracy for obtaining the target hematocrit ($r = 0.75$, $P < 0.05$).

Based on an initial hematocrit of 40% and a target hematocrit of 22%, the range of blood that can be harvested from patients with 10 to 80 kg of body weight ranges from approximately 375 to 3000 mL. If the initial hematocrit is less than 35%, insufficient blood can be withdrawn to realize the advantages of hemodilution. Therefore, two practical problems emerge: (1) excess administration of intravenous fluid prior to hemodilution will result in hypervolemic hemodilution without the benefit of withdrawing blood; and (2) patients who have donated autologous blood in a predeposit program may come to surgery with a hematocrit in the range of 32% to 37%, therefore, the volume that can be withdrawn is limited. The latter problem may be averted if recombinant human erythropoietin is used in the predeposit phase. This would allow the number of units collected preoperatively[20] to be increased; furthermore, these patients could be candidates for hemodilution. Therefore, even in cases of major surgery, including major reconstructive orthopedic surgery, the combination of predeposit and acute normovolemic hemodilution could potentially eliminate homologous blood and component administration.

Autologous blood is stored in the operating room at room temperature in order to ensure functional platelets. This autologous blood should be labeled as "autologous donor," with the patient's name, hospital medical record number, and date and time of withdrawal. Fresh autologous blood should be administered within 4 to 6 hours of withdrawal; however, at this time there are no explicit guidelines.[2, 12] In practice, the autologous blood is reinfused after completion of major surgical blood loss and establishment of hemostasis, in the *reverse* order in which the units were collected (increasing hematocrit). The goal is to obtain an early postoperative hematocrit of 28% to 30% with optimal intravascular volume. Where possible, we have combined hemodilution with a predeposit program. To maintain the target hematocrit of 22 vol% during surgical blood loss, we infuse the *predeposited* blood in the *same order* in which it was collected (i.e., the oldest first).

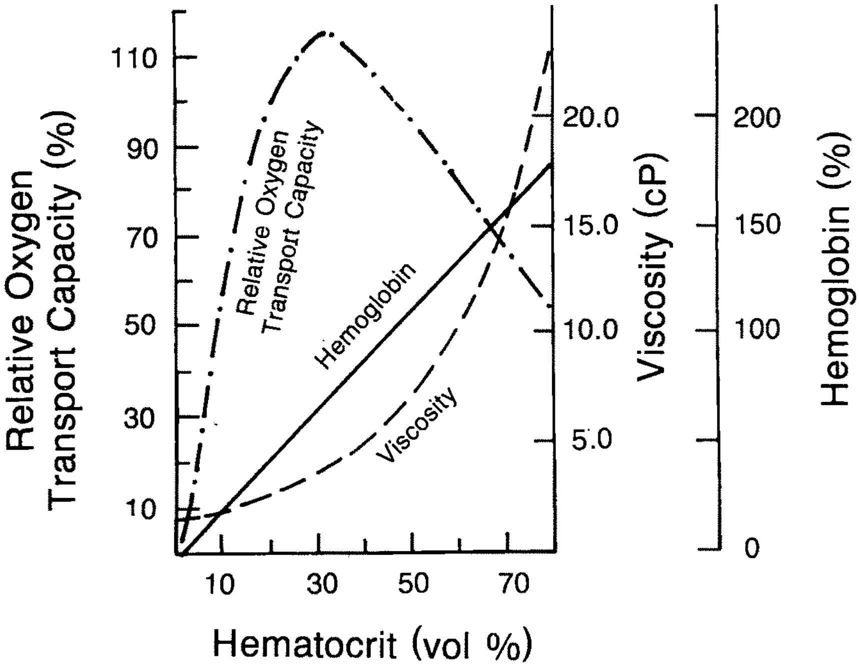

Figure 1. Relationship between hematocrit and oxygen transport capacity: Systemic oxygen transport capacity as a percent of control, viscosity (cP centipoise), and hemoglobin (percent of control) as a function of hematocrit (vol %) during normovolemic hemodilution and hemoconcentration. (*Modified from* Hint H: The pharmacology of dextran and the physiological background for clinical use of Rheomacrodex and Macrodex. Acta Anaesthesiol Belg 19:119, 1968; and *from* Wood JH, Kee DB Jr: Hemorheology of the cerebral circulation in stroke. Stroke 16:768, 1985; with permission of the American Heart Association, Inc.)

Physiology of Acute Normovolemic Hemodilution

Rheology. The safety of hemodilution depends on the direct exponential relationship between the hematocrit and blood viscosity and the non-Newtonian characteristics of blood viscosity. Unlike Newtonian fluids, the viscosity of blood varies inversely with the flow rate. Thus, the normal hematocrit of 42 to 45 vol% provides optimal oxygen transport only at high flow rates. Therefore, hemodilution significantly reduces the blood viscosity, with the greatest decrement in low flow vessels and from a hematocrit within the normal range to 30 vol%. In addition, under normovolemic conditions and with a hematocrit in the range of 25 to 30 vol%, oxygen transport is considered to be optimal (Fig. 1), and the increase in cardiac output and organ blood flow are primarily the result of the decrease in blood viscosity.[29, 31, 49, 50, 61, 77] With further reduction in hematocrit to the range of 20 to 24 vol%, oxygen transport approximates that within the normal hematocrit range (Fig. 1). Additionally, during mild and moderate hemodilution, provided that volume replacement is adequate and maintained, cardiovascular and respiratory reflexes do not contribute substantially to the maintenance of oxygen transport.

Oxygen Transport. Acute normovolemic hemodilution may result in three groups of compensatory changes that maintain oxygen delivery: (1) an increase in cardiac output and critical organ blood flow (cerebral, myocardial, and renal); (2) an increase in oxygen extraction; and (3) a possible decrease in the hemoglobin affinity for oxygen. However, a number of pathophysiologic or induced changes may impair oxygen delivery, including inadequate maintenance of volume replacement, induced or inadvertent hypotension, and hypocapnia.

Hemodynamic and Oxygen Transport Responses to Hemodilution. The immediate hemodynamic response to moderate ANH (hematocrit of 20 to 25 vol%) is increased central venous pressure, decreased heart rate[19, 34, 40, 49, 50] (Fig. 2), increased cardiac output, and decreased systemic vascular resistance.[19, 30, 40, 45, 64]

However, hemodynamic and oxygen transport changes throughout surgery with hemodilution show a wide variation, and in most studies where comprehensive data were obtained throughout surgery, after the initial increase in oxygen transport, the cardiac output, O_2 delivery, and oxygen consumption decreased to a plateau.[30] These changes are associated with increased oxygen extraction and arteriovenous oxygen difference.[30, 64] Reinfusion of blood to a hematocrit of 29 vol% leads to a reversal of the cardiac output and oxygen delivery to prehemodilution values.[30] Unlike experimental studies, the interpretation of these clinical studies is complicated by concurrent surgery, variations in level of painful stimuli, depth and duration of anesthesia, and adjuvant cardiovascularly active drugs that include local low-dose epinephrine at the wound site and systemic vasodilators. Although our patients were anesthetized primarily with an opioid infusion, the magnitude of stimuli varied greatly during spinal fusion. All patients in our series recovered without any neurologic or neuropsychiatric sequelae.[30, 34]

Organ Blood Flow and Function During Hemodilution. Several experimental studies have examined the effects of hemodilution together with deliberate hypotension on organ blood flow (renal, myocardial, and cerebral blood flow).[16, 59, 63] Consistently, a combination of hemodilution and hypotension has reduced oxygen delivery to the brain and the renal cortex.[16, 59, 63] During adenosine-induced hypotension, the direct vasodilatation of the coronary arteries has led to coronary blood flow and oxygen delivery exceeding the prevailing metabolic requirements.[16] An inverse relationship between hematocrit and cerebral blood flow, consistent with the changes in viscosity[77] and autoregulation[10] of the cerebral circulation, has been demonstrated in dogs anesthetized with pentobarbital[46] (Fig. 3). Therefore, as shown in Figure 4, increased hemodilution is associated with increased dependence of the cerebral blood flow on the mean arterial pressure. At a hematocrit of 20 vol%, some vasodilatation is present; at a hematocrit of 5 vol%, this is maximized. In the absence of hypotension (mean arterial pressure, 60, 80, and 100), electroencephal-

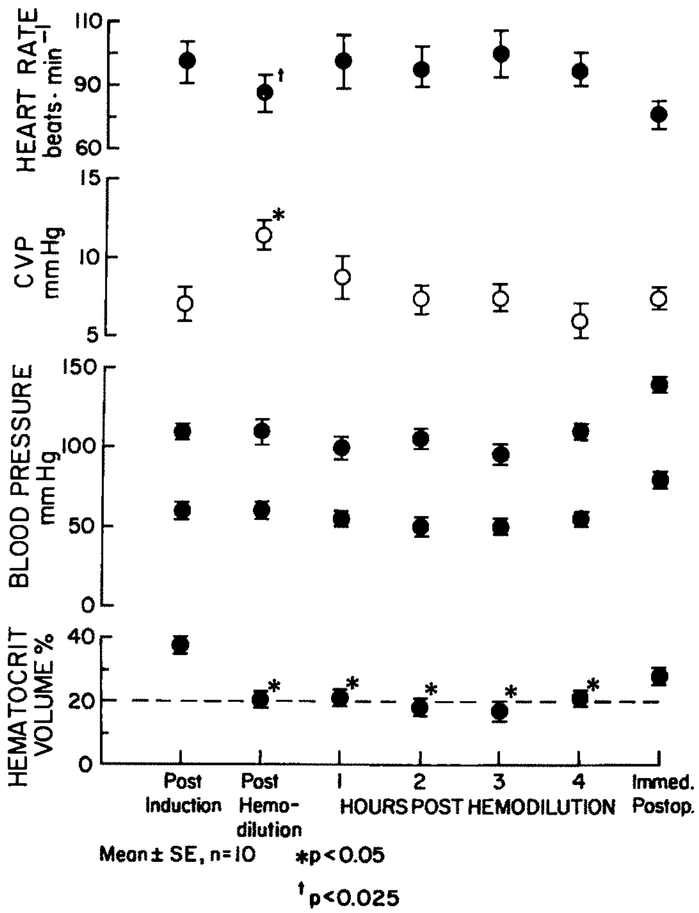

Figure 2. Hemodynamic response to acute normovolemic hemodilution and surgery: heart rate, central venous pressure (CVP), arterial blood pressure, and hematocrit responses to hemodilution in patients undergoing reconstructive surgery for scoliosis (n = 10, age 11.7 ± 1.1 years and weight 40.8 ± 4 kg). Statistical significance of differences are from postinduction and prehemodilution values; $*P < 0.05$ and $\dagger P < 0.025$. (*From* Kafer ER: Acute intraoperative hemodilution with autologous blood transfusion. Perioperative Red Cell Transfusion NIH Consensus Conference, June 27–29, 1988, Bethesda, MD, pp 65–69, with permission; and Kafer ER, Isley MR, Hansen T, et al: Automated acute normovolemic hemodilution reduces homologous blood transfusion requirements for spinal fusion. Anesth Analg 65:S76, 1986; with permission of the International Anesthesia Research Society.)

ographic (EEG) frequencies and amplitudes have been essentially unchanged even with extreme hemodilution (40 to 5 vol%); however, at a mean arterial pressure of 40, there have been increasing changes in both frequency and amplitude of EEG tracings, consistent with cerebral ischemia (decreased frequency and amplitude). The cerebral metabolic rate has paralleled those changes.[46] In severe hemodilution to 10 to 15 vol% in anesthetized primates (baboons), somatosensory

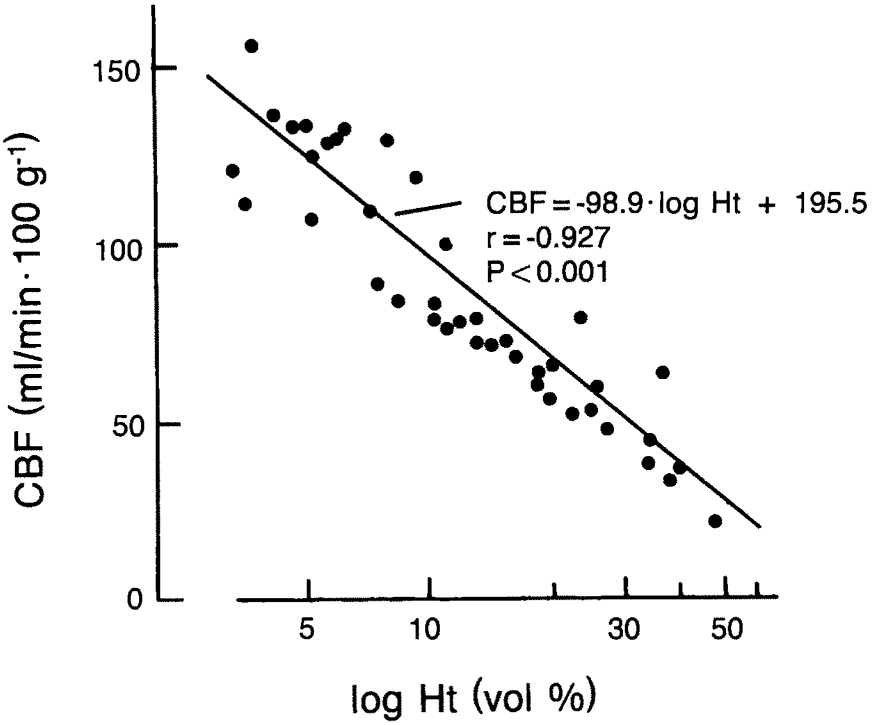

Figure 3. The relationship between log hematocrit volume percent (log Ht vol %) and the cerebral blood flow (CBF) at mean arterial pressure (MAP) of 100 mm Hg in pentobarbital anesthetized dogs. (*Modified from* Maruyama M, Shimoji K, Ichikawa T, et al: The effects of extreme hemodilution on the autoregulation of cerebral blood flow, electroencephalogram and the cerebral metabolic rate of oxygen in the dog. Stroke 16:675–679, 1985; with permission of the American Heart Association, Inc.)

cortical-evoked potentials (SCEPs) latencies have been prolonged; and at a hematocrit of less than 10 vol%, the latencies have been prolonged and the amplitudes of SCEPs and visually evoked potentials have been reduced.[55]

Oxyhemoglobin Dissociation Curve. The delivery of oxygen to the tissues of critical organs (brain, myocardium, and liver) may be enhanced by increased organ and microcirculatory flow, which reduces diffusion distance, and a possible increase in the P_{50}.[58] However, an increase in the P_{50} and erythrocyte 2,3 diphosphoglycerate (2, 3 DPG) is only observed with extreme hemodilution below 15%.[68] Therefore, the consensus is that this compensatory mechanism of an increase in P_{50} is not operative in acute mild to moderate hemodilution. Nevertheless, it should be noted that reinfusion of fresh autologous blood results in a higher post-transfusion P_{50} in comparison with transfusion of stored whole blood (P_{50}, 28.4 ± 0.46 vs 24.7 ± 0.30; $P < 0.002$).[58]

Platelets and Coagulation Factors. Acute hemodilution reduces platelet counts and the concentration of fibrinogen.[3, 39] As Betts et al[3]

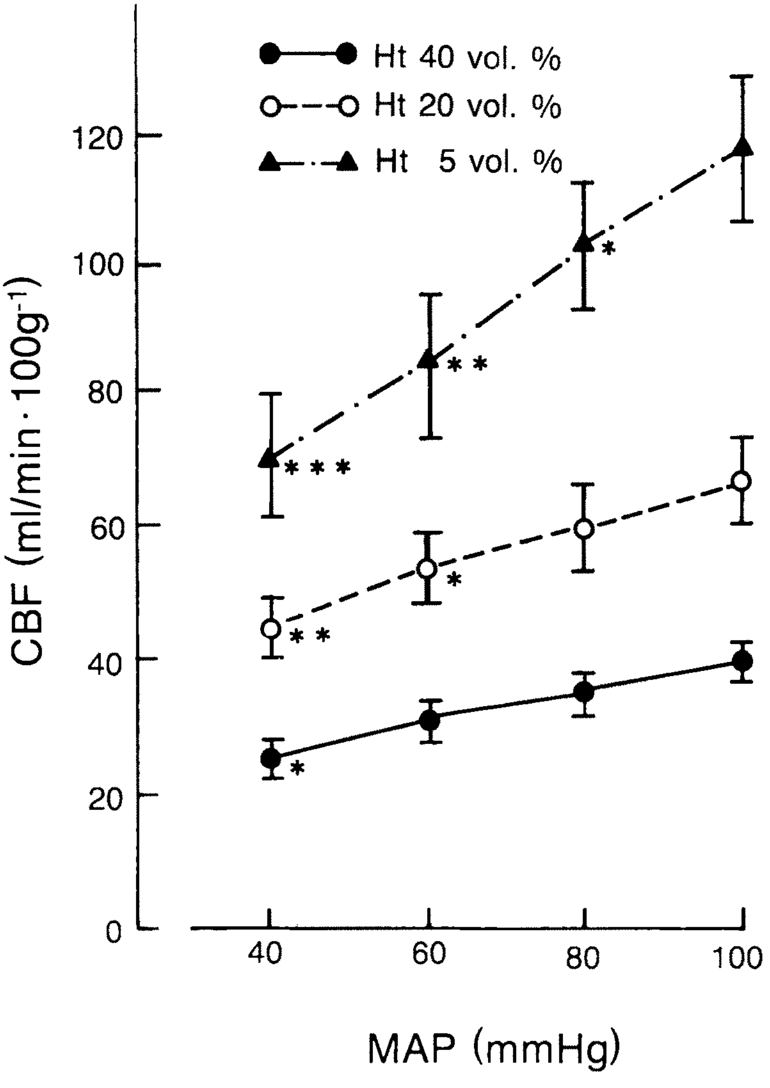

Figure 4. Autoregulation of the cerebral circulation: The relationship between the mean arterial pressure (MAP) and cerebral blood flow (CBF mean ± SEM) at 40% (●), 20% (○), and 5% (▲) hematocrit (Ht vol %) values in the pentobarbital-anesthetized dogs. The value accompanied by asterisks denotes a significant difference from the value at a MAP of 100 mm Hg ($*P < 0.05$, $**P < 0.01$, $***P < 0.001$). (*Modified from* Maruyama M, Shimoji K, Ichikawa T, et al: The effects of extreme hemodilution on the autoregulation of cerebral blood flow, electroencephalogram and the cerebral metabolic rate of oxygen in the dog. Stroke 16:675–679, 1985; with permission of the American Heart Association, Inc.)

observed in children with hemodilution to 27 vol%, the platelet counts and fibrinogen levels were 90% and 60% of prehemodilution values, respectively. The increases of prothrombin time (PT) and partial thromboplastin time (PTT) to 113% and 117%, respectively, were statistically significant only for the PT. Additionally in Betts et al's[3] study, although the patients also received homologous blood, after reinfusion of the fresh autologous blood, the prolongation of the PT and PTT resolved. Milam and associates,[51] in 1985, observed that moderate hemodilution (hemoglobin less than 10 g/dL) together with autologous blood transfusion in children with cyanotic congenital heart disease reduced blood loss and the subsequent requirement for blood, platelets, cryoprecipitate, and fresh frozen plasma. Further, only 14% of those patients with moderate hemodilution were reoperated on, as compared with 40% of those with mild hemodilution (hemoglobin greater than 10 g/dL).

Clinical Application of Acute Intraoperative Hemodilution. During the last two decades, ANH with reinfusion of autologous blood has been utilized in four areas: (1) in cardiac surgery to decrease viscosity during hypothermia with cardiopulmonary bypass; (2) in cardiac surgery to minimize coagulopathy and bleeding, especially in cyanotic congential heart disease[51, 54]; (3) in Jehovah's Witness patients, for whom harvesting of blood and reinfusion is an acceptable method; and (4) in noncardiac surgery with or without combination with predeposit and/or intraoperative and postoperative salvage. This discussion will focus on the fourth clinical application of hemodilution. The management of Jehovah's Witness patients is discussed in the article by Rothenberg in this issue.

During the last decade, hemodilution (normovolemic, isovolemic, and euvolemic) has been used primarily to minimize homologous blood and component transfusion, alone or in combination with predeposit[32] and with blood salvage.[14, 15, 47, 71] The age, and therefore body weight and blood volume, of patients has ranged from infancy (25 days old, 3 kg; and 8 months old, 10 kg)[38, 65] to adults. The surgical categories include cardiac surgery, orthopedic surgery (particularly reconstructive surgery for scoliosis[34, 39, 45, 72] and hip arthroplasties in the elderly[19, 64]), gynecologic and urologic surgery for cancer,[45] and major vascular surgery.[15] Many reports are anecdotal or retrospective, and only a few prospective studies examined the safety and efficacy of ANH and compared the outcome of those patients with that of control patients. These prospective studies were designed to minimize homologous blood and component transfusions before predeposit programs were established or effective.

Schaller and associates,[65] who have probably the largest clinical experience, studied over 300 patients who underwent ANH from 1974 to 1983. In 1983, they reported on 25 patients who had 27 operations successfully utilizing ANH (52% under the age of 10 years; the youngest, 25 days old and weighing 3.1 kg). They reported that only 6 of 25 patients required homologous blood. Cutler,[15] reporting a large series of patients (n = 106) who underwent major vascular surgery, showed that the use of a combination of ANH, RBC salvaging, and blood con-

Table 1. *The Efficacy of Acute Intraoperative Normovolemic Hemodilution With Autologous Blood Transfusion**

	HOMOLOGOUS BLOOD COMPONENTS				
SERIES	*Blood Loss* *(L)*	*PRBC* *(U)*	*FFP* *(U)*	*Platelets* *(U)*	DURATION OF SURGERY *(h)*
Retrospective	5.49	8.6	1.8	1.2	8.03
(n = 10)	±0.98	±1.6	±0.7	±0.8	±0.52
Prospective					
ANH	1.70	<1.0	0	0	5.68
(n = 10)	±0.39	0	0	0	±0.54
P value	<0.0005	<0.001	<0.025	<0.01	<0.01

Abbreviations: ANH = acute normovolemic hemodilution; PRBC = packed red blood cells; FFP = fresh frozen plasma.

* Values are mean ± SE.

Adapted from Kafer ER, Isley MR, Hansen T, et al: Automated acute normovolemic hemodilution reduces homologous blood transfusion requirements for spinal fusion. Anesth Analg 65:S76, 1986; with permission of the International Anesthesia Research Society.

serving surgical technique reduced homologous blood transfusion, as compared with a historic series. Kafer and associates[33, 34] examined the efficacy of ANH in a prospective series of patients undergoing reconstructive surgery for scoliosis (most cases were idiopathic and exclusive of meningomyelocele). The treatment group was matched in age, body weight, and magnitude of surgery to a retrospective group without hemodilution. ANH with autologous blood transfusion reduced blood loss, the number of homologous units of blood and components administered, and the duration of surgery (Table 1).

Anesthetic Management and Monitoring. Both the anesthetic management and monitoring required depend on the type and magnitude of surgery, patient status, and coexistent disease. Because the majority of our patients now have neural electrophysiologic monitoring (computer-processed EEG or SCEPs), we have developed anesthetic techniques based on continuous infusions of opioids (e.g., sufentanil) supplemented by isoflurane. Neuromuscular blockade is also usually maintained using a continuous infusion of atracurium monitored by a nerve stimulator. An $\mathrm{FIO_2}$ (fraction of inspired oxygen) of 1 not only provides additional dissolved oxygen but also reduces the oxygen consumption[13] and, therefore, by reducing demand, contributes to safety. Normocapnia is maintained with conventional mechanical ventilation. In general, we limit induced hypotension to an MAP of 60 to 65 mm Hg or higher in older patients and at the same time optimize vascular volume, central venous pressure, and urine flow. Both continuous and discontinuous monitoring are critical to safe hemodilution (Table 2). Arterial blood gases and the hemoglobin or hematocrit should be regularly measured at the same time that blood loss is evaluated to ensure that the hematocrit, hemodynamic status,

Table 2. *Recommended Standard and Selected Physiologic Monitoring for Acute Intraoperative Hemodilution*

- Continuous monitoring
  - Standard
    - ECG:V_5 II
    - Respired gas analysis
      - Oxygen
      - CO_2
      - Anesthetic gases
    - Pulse oximetry
    - Arterial blood pressure
    - Central venous pressure
    - Urine flow
    - Raw and computer-processed EEG*
  - Selected patients
    - Pulmonary artery pressures
    - Cardiac output with calculated hemodynamic and oxygen transport profiles
    - Somatosensory evoked responses
- Discontinuous
  - Arterial blood gases
  - Hemoglobin or hematocrit
  - Electrolytes
  - Coagulation profile

* Facilitates continuous monitoring of depth of anesthesia as well as adequacy of cerebral oxygenation.

and oxygen transport provide the patient with an adequate margin of safety.

Advantages and Limitations. As with any modality, ANH has advantages and limitations (Tables 3 and 4). The advantages include optimization of critical organ perfusion and oxygen delivery; reduction or elimination of homologous blood and component transfusions; reduction of surgical blood loss; reinfusion of fresh whole blood with functional platelets; application to a wide range of surgeries, patients, age, and physical condition; and utilization upon short notice or when the patient declines or is unable to participate in a predeposit program. There are several limitations: the technique is limited to cases in which the initial hematocrit is greater than 35%; the target hematocrit should not be lower than 20 to 25 vol%; relative contraindications include severe coronary artery disease, severe aortic or pulmonic valve stenosis, congestive cardiac failure, major organ system insuf-

Table 3. *Advantages of Acute Intraoperative Hemodilution With Autologous Blood Transfusion*

- Hemodilution optimizes critical organ perfusion and oxygen delivery
- Reinfusion of fresh whole blood therefore reduces not only homologous RBCs but also component transfusion
- Reduces blood loss
- Applicable in a wide range of surgeries, patient ages, and coexistent disease
- Applicable in elective and emergent surgeries
- Combines with predeposit programs and intraoperative salvage

Table 4. *Restrictions and Relative Contraindications to Acute Intraoperative Hemodilution*

Limits of acute normovolemic hemodilution
  Hemoglobin > 7 g/dL
  Hematocrit range, 20–25 vol%
Limited to patients whose body weight is > 10 kg
Relative medical contraindications
  Severe coronary artery surgery
  Severe aortic or pulmonic stenosis
  Congestive cardiac failure
  Major organ system insufficiency
  Impaired coagulation
  Anemia
  Pulmonary insufficiency that limits intraoperative or postoperative oxygenation, i.e., large AaO_2D
Relative surgical contraindications
  Surgery with anticipated rapid and massive blood loss

Abbreviation: AaO_2D = Calculated alveolar-arterial oxygen difference breathing air or oxygen.

ficiency, impaired coagulation, and pulmonary insufficiency where the alveolar-arterial oxygen difference breathing air or oxygen would preclude adequate oxygenation during anesthesia or in the postoperative period (Table 4). (Although a number of studies reported successful ANH in infants weighing less than 10 kg, in patients of such low weight there is an insufficient margin of safety to estimate blood loss accurately enough to prevent unsafe reduction in oxygen transport.[32]) Finally, where blood loss is anticipated to be massive, we do not recommend hemodilution as either a safe or efficacious modality. The most serious practical monitoring limitation is the absence of a continuous monitor of hemoglobin concentration or hematocrit. A number of issues and problems related to the selection, management, and monitoring of patients undergoing ANH and surgery are summarized in Table 5.

PERIOPERATIVE SALVAGE

Perioperative blood salvage involves the recovery of shed blood from the surgical or traumatic site or the residual erythrocytes in the oxygenator and the reinfusion of the processed or unprocessed blood. Although perioperative blood salvage and reinfusion is the oldest form of autologous blood transfusion, its use prior to the early 1970s was limited. As a result of concern for the heavy use of blood resources in cardiac surgery and to conserve the residual oxygenator erythrocytes, several groups evaluated devices to salvage and process blood. The most successful was the application by Orr[56] of existing RBC processing technology (Cobe Cell Washer and subsequently Haemonetics Model 15 [Braintree, MA] discontinuous flow centrifuge).

Table 5. *Problems and Issues of Acute Intraoperative Normovolemic Hemodilution*

- Selection of type of surgery
- Patient selection
  - Relative contraindications
- Optimal hemodilution
  - Procedure
    - Speed
    - Accuracy
    - Safety
  - Optimal cell-free substitute and ratio to blood withdrawn
  - Safe target hemoglobin concentration
- Optimal anesthetic management
- Optimal patient monitoring
  - Standard noninvasive and invasive monitoring
  - Electrophysiologic monitoring of brain and spinal cord
  - Noninvasive measurement of cardiac output
  - Continuous hemoglobin or hematocrit measurement
- Quantification of safe limits and at-risk organ systems
- Evaluation of coexistent patient pathophysiologic variables
  - Induced hypotension
  - Hypocapnia
  - Hypoxemia

Currently, two forms of perioperative salvage are available: recovery of shed blood from the site of loss or from the oxygenator, followed by processing and reinfusion of the concentrated washed erythrocytes, and recovery of blood from the site of loss, particularly a cavity, into a canister or bag, followed by filtration and reinfusion as whole blood.

Red Cell Salvaging With Processing

Intraoperative RBC salvaging and processing was introduced by using a device designed for deglycerolizing frozen erythrocytes[57] (Haemonetics, Natick, MA). The blood was anticoagulated upon removal from the wound and within 10 minutes 375 mL of washed erythrocytes were available. The product was equivalent to washed homologous packed red blood cells, and preliminary evaluation showed no evidence of coagulopathy. During the last decade, an increasing number of manufacturers has offered blood salvaging and red cell processing devices.

Instrumentation and Technique. A centrifuge-based erythrocyte salvage instrument consists of a double lumen suction wand with an anticoagulant adding system (Fig. 5; wand only), anticoagulant (62 to 65 mL CPD/450 mL blood), vacuum system and reservoir (e.g., cardiotomy type with 120-μ filter), saline washing solution, pump, centrifuge (range of sizes), and bags for processed erythrocytes (Fig. 6)[60, 75] (e.g., Haemonetics Cell Saver, Haemonetics Corp., Braintree, MA; Electromedics, Englewood, CO; Cobe, Lockwood, CO; Sorenson Autotransfusion Devices, Salt Lake City, UT). The centrifuge is used for RBC washing with saline and concentrating. The saline-washed

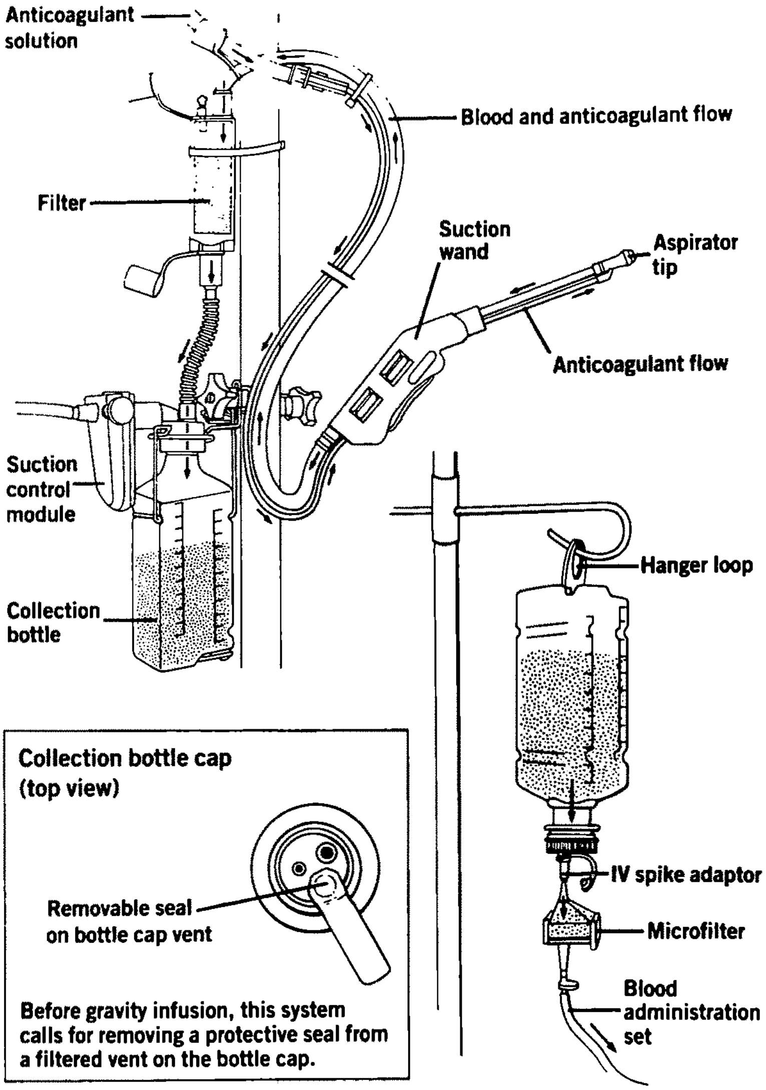
Anticoagulant solution
Blood and anticoagulant flow
Filter
Suction wand
Aspirator tip
Anticoagulant flow
Suction control module
Collection bottle
Hanger loop
Collection bottle cap (top view)
Removable seal on bottle cap vent
Before gravity infusion, this system calls for removing a protective seal from a filtered vent on the bottle cap.
IV spike adaptor
Microfilter
Blood administration set

Figure 5. Operative salvage: Blood aspirated from a wound is anticoagulated (e.g., citrate-phosphat-dextrose-adenine [CPDA-1]) using a dual-channel suction wand with a macro-filter (265-μ macro-filter), and collected in a container for reinfusion (e.g., Intra-Op Autotransfusion System, Davol, Inc., Cranston, RI). The salvaged blood is infused using a blood administration set and a 20- and 40-μ filter. (*From* Butler S: Current trends in autologous blood transfusion. RN November 1989, pp 44–54; with permission.)

and processed blood is collected in "reinfusion" bags, appropriately labeled (autologous use only, patient's name, medical record number, date and time of collection), and delivered to the anesthesiologist for administration with a blood administration set (20- or 40-μ filter). All plasticware that comes in contact with the blood is disposable and is provided as a set by the manufacturer (e.g., Surgical Blood Management Kit—disposable, Electromedics). Blood is not transfused directly from the centrifuge system in order to avoid the risk of air embolism.[75] Salvaged blood should be administered immediately. Storage is controversial and a planned approach in consultation with the transfusion service is recommended.[2, 12] Blood salvaging and processing systems are microprocessor controlled with manual modes and provide rapid recovery and processing of blood. For example, 225 mL of washed, saline-suspended erythrocytes (hematocrit, 55 vol%) can be prepared in 3 to 4 minutes, provided the reservoir contains sufficient erythrocytes. Where blood loss is large and rapid, as in liver transplantations, the capacity can be increased by doubling the number of reservoirs.[75]

Efficacy and Safety. The efficacy of red cell salvaging and processing measured as percent of estimated blood loss recovered or reduction in perioperative homologous blood administration varies both with and within type of surgery. During the last decade, several prospective studies have demonstrated that perioperative salvage with processing and autotransfusion either eliminated or reduced homologous blood transfusion in both emergency and elective surgery. The surgical procedures include major vascular surgery,[15, 24, 35] cardiac surgery including myocardial revascularization,[6, 9, 14, 47, 60, 71] spinal fusion,[44, 62] both intraoperative and postoperative salvage for hip arthroplasty,[21, 66] and liver transplantation.[75] Additionally, in Keeling's series,[35] another 5.9% included exploratory laparotomy, hysterectomy, cesarean section, ectopic pregnancy, and other procedures. Popovsky and associates[60] emphasize that the efficacy in reducing homologous blood transfusion in cardiac surgery with cardiopulmonary bypass is greatly improved by concentrating the residual in the oxygenator.

Extensive prospective studies examining coagulation profiles, fibrinogen, fibrin split products, free hemoglobin, platelet counts with RBC salvaging, and processing have been reported. These reports confirm that salvaging with processing using modern technology does not impair hemostasis more than anticipated from the same magnitude of homologous blood transfusion.[6, 24, 35, 75] Breyer and associates[9] also demonstrated that the number of fresh frozen plasma and platelet units were not increased by RBC salvage with processing. However, Boldt and associates[6] claimed that hemofiltration of residual oxygenator blood resulted in a more rapid recovery of coagulation profiles, and they argue that this was because the plasma protein fraction was not lost. In contrast, Griffith and associates[22] observed that RBC washing in comparison with unprocessed blood shed from the mediastinum reduced the biochemical evidence of coagulopathy. RBC salvaging and processing does increase free hemoglobin, resulting in decreased haptoglobin in the recipient.[27] The magnitude of these changes was unrelated to the volume transfused, and in individual cases the free hemoglobin was high. While this observation does not contraindicate transfusion of processed salvaged RBCs, measures to optimize renal function are recommended. In addition, several studies have demonstrated that the survival of transfused chromium-tagged erythrocytes was similar for processed salvaged erythrocytes and homologous blood.[62]

Autotransfusion of Unprocessed Salvaged Blood

The perioperative recovery of shed blood from pleural or peritoneal cavities and from the mediastinum with reinfusion after filtering has been used for trauma, other emergencies such as ectopic pregnancies, and cardiac and thoracic surgery. The devices include the system illustrated in Figure 7, which is designed to collect blood per-

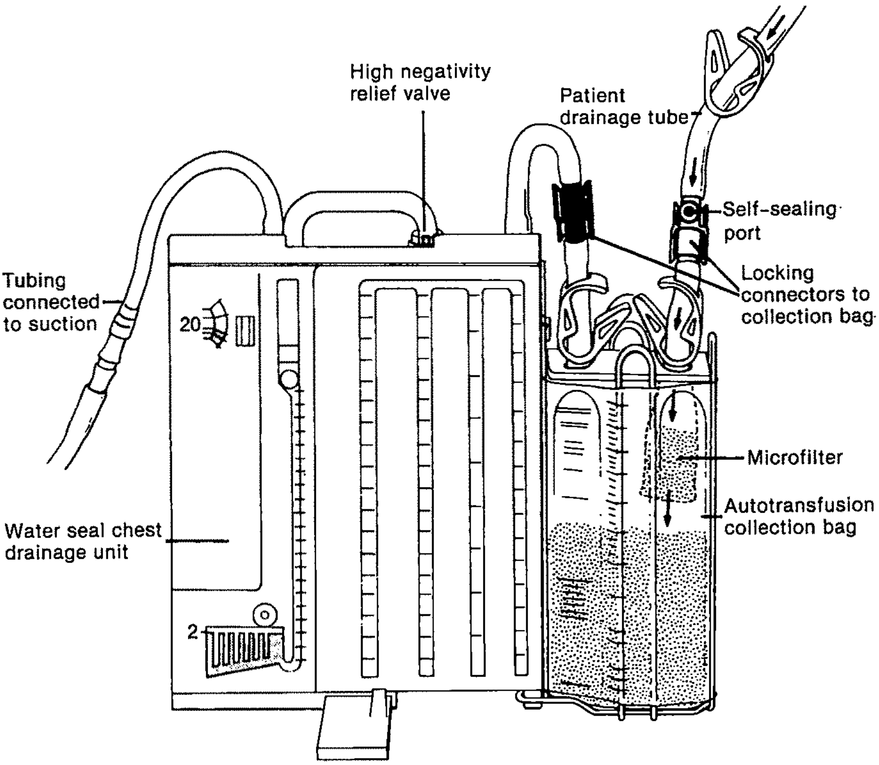
High negativity relief valve
Patient drainage tube
Self-sealing port
Locking connectors to collection bag
Tubing connected to suction
20
Microfilter
Autotransfusion collection bag
Water seal chest drainage unit
2

Figure 7. Perioperative salvage using a closed system: Blood lost into a cavity, e.g., pleural, as a result of a chest injury or following cardiac surgery, is drained via a macrofilter into a collection bag. Through large-bore chest tubes the collection system is connected to a water-seal drainage system (e.g., Pleur-evac Chest Drainage System, Deknatal, Fall River, MA). In the system shown the flexible insert containing the filtered blood is removed and the salvaged blood is infused using a blood administration set with a 20- or 40-μ filter. (*From* Butler S: Current trends in autologous blood transfusion. RN November, 1989, pp 44–54; with permission.)

ioperatively from the pleural cavity (Pleur-evac Chest Drainage System, Deknatal, Fall River, MA; also Chest Drainage System, Electromedics; Thora-Klex Chest Drainage Autotransfusion System, Davol, Cranston, RI). Similar devices have also been developed for shed mediastinal blood (e.g., Sorenson Drainage System, Sorenson Research Corp.) Blood recovered with these systems is administered using a blood administration set and a microaggregate filter (20 or 40 μ). Blood recovered from serous cavities or the mediastinum is usually defibrinated and therefore does not require anticoagulation. However, if the blood loss is rapid or clots appear, then anticoagulant should be added (e.g., CPDA:blood ratio, 1:10). Shed blood may also be collected from a wound, as illustrated by the system in Figure 5. This system involves simultaneous anticoagulation as in the RBC processing technique (Intra-Op Autologous Blood Collection, Davol, Inc.). Other systems include a collection system using a Yankauer-type sucker with integral filter (260 μ) and collection bag preloaded with anticoagulant mounted in a plastic shell with vacuum system connection (Solcotrans Autologous Whole Blood Transfusion System, Solco Basle, Rockland, MA). The recommendations for aspiration from a wound include aspiration of a pool of blood; agitation of collected blood to mix anticoagulant; avoidance of turbulence, which may cause hemolysis; and the availability of alternate suction systems to aspirate surface bleeding and irrigation fluids. Blood is reinfused directly from the collecting bag using a blood administration set and a 20- or 40-μ filter. The contraindications to the use of these systems include malignancy, bacterial contamination, contamination with fluid at the surgical site unsuitable for transfusion, the presence of hemostatic substances such as Ativene (Alcon Surgical) or absorbable gelatin sponge, and sterilizing fluid within the wound, e.g., povidone-iodine.

The advantages of recovering shed blood and reinfusing the unprocessed product include simplicity, lack of capital outlay for instrumentation, and lack of need of specially trained staff to operate an RBC processor. Therefore, blood salvaging with autotransfusion has an important role in surgical emergencies with major blood loss and where the technology and personnel are not available. In less extreme situations, recovery of shed blood and its reinfusion may have a role; however, although its use has reduced homologous blood utilization, there is concern for possible coagulopathy or the inappropriate administration of coagulation factors and platelets. Griffith and associates observed that the presence of fibrin-split products even without other evidence of disseminated intravascular coagulation could confuse the interpretation of tests for this type of coagulation. Therefore, Griffiths recommends that, where possible, shed blood or blood recovered from a wound should be washed before reinfusion.

Advantages and Limitations of Perioperative Salvage

Perioperative salvage is widely applicable and is unrestricted by age, body weight, or most coexistent diseases; may be combined with predeposit and hemodilution; is advantageous and may be lifesaving in emergency surgery in which blood banking resources are limited; requires minimal institutional and logistical health care support services; and is generally safe, efficient, and cost effective.[9] Perioperative salvage, in particular without processing, is applicable where health care resources are limited or in mass disasters. The major limitation is that the effective component is limited to erythrocytes. Also, the patient should be monitored for coagulopathy and the appropriate coagulation components should be replaced. Therefore, although blood salvage and autotransfusion may reduce the number of homologous RBC units, these techniques do not eliminate the complications of homologous blood component replacement.

The potential for systemic dissemination of malignancy from reinfusion of tumor cells has curtailed the application in surgical oncology.[18, 37] However, although Klimberg et al[36, 37] question the evidence supporting this restriction and report follow-up studies in patients with malignancy who survived after RBC salvage, the consensus regards malignancy as a contraindication to perioperative RBC salvage and autotransfusion. Septicemia and infection at the site of surgery is also regarded as a contraindication to RBC salvage and autotransfusion. Using in vitro inoculated (*Escherichia coli*) blood, Bourdreaux and associates[7] demonstrated that washing reduced the bacterial count and that the reduction was inversely related to the original count (range, 23% to 15%). Although further laboratory studies are required to determine the levels of bacterial contamination that can be tolerated for immediate autotransfusion, RBC salvaging and processing, even in contaminated peritoneal blood, may be lifesaving where there is no alternative.[23]

1990s PERSPECTIVE

Blood transfusion practices now offer an increasing array of alternatives. Each alternative has advantages, disadvantages, limitations for patient, type of surgery, and health care environment, as well as differing immediate, institutional, and long-term costs. For each specific patient the surgeon, anesthesiologist, and transfusion physician should review the plans and alternatives both to optimize patient care and to minimize exposure to homologous blood and components. In the elective patient, all three modes of autologous blood transfusion, predeposit including component preparation, hemodilution, and RBC salvaging, may have a role.[71] In the emergent situation, the alternatives are limited to hemodilution and salvaging whereas in an emergency, usually only RBC salvaging with or without processing is appropriate. As has been reported, in predeposit programs, there is underutilization of both hemodilution and RBC salvaging.[71] While each institution and surgical speciality varies in its philosophy and practice, increasing emphasis should be placed on the more general use of autologous blood transfusion.

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Alternatives to Transfusion Therapy

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Efforts to produce a clinically acceptable hemoglobin solution that could function as a temporary oxygen carrier have evolved through several stages. Beginning with the simple tetramer, we have lowered the affinity state by pyridoxylation and then polymerized the modified tetramer. This new substance, polyhemoglobin, has a normal oxygen capacity and a half-life of 38 hours. Issues of nephrotoxicity and immunocompetence after infusion remain to be defined.

For more than a decade we have been interested in the concept that hemoglobin solution might serve as a temporary substitute for the red blood cell. This interest is based on several remarkable characteristics of the hemoglobin molecule. First, hemoglobin has the capacity to bind oxygen. One gram of hemoglobin can chemically bind 1.3 cc of oxygen. Few, if any, biologically acceptable substances have a greater oxygen capacity at physiologic pressures. Second, the hemoglobin molecule has the ability to become fully saturated for oxygen at ambient oxygen pressures. Thus, hemoglobin can be fully effective as an oxygen carrier without the addition of extra oxygen to the inspired air. High concentrations of inspired oxygen are known to produce serious lung injury.[10] Third, oxygen is normally unloaded from hemoglobin in the capillary at oxygen pressures of approximately 40 torr. This unloading characteristic allows oxygen molecules to flow from hemoglobin to the intracellular mitochondria without producing interstitial hypoxia.

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HEMOGLOBIN SOLUTION: AN EFFECTIVE OXYGEN CARRIER?

In 1934, Mulder et al[13] published a classic study that was unfortunately ignored for more than 30 years. They measured oxygen consumption in dogs and cats breathing room air before and after total exchange transfusion with hemoglobin solution. The results are shown in Figure 1. Mulder and associates were the first to report no change in oxygen consumption at zero hematocrit with hemoglobin

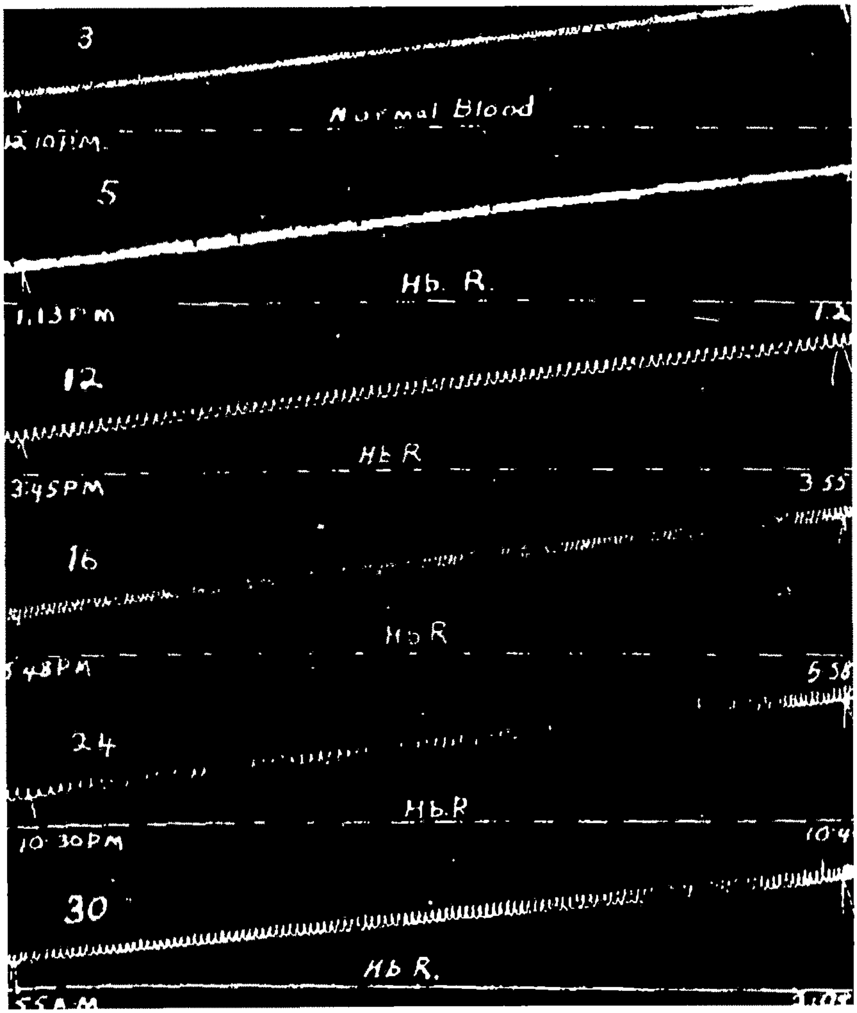

Figure 1. Original smoked drum recording of respiratory excursion of a cat during exchange transfusion with hemoglobin solution. The slope of the line represents oxygen consumption. Panel 3 is the control. All the subsequent panels represent measurements made after total exchange transfusion. There is no change in oxygen consumption at zero hematocrit.

Table 1. *Properties of Hemoglobin-Saline Solution*

Hemoglobin concentration	6–9 g/dL
Methemoglobin	2%–4%
Total phospholipids	<1 mg/dL
pH	7.36–7.45
P_{50}	14.0 torr

solution. In addition, they reported that following total exchange transfusion, cats were capable of landing on their feet when dropped in an upside-down position from a modest height.

In 1976, we repeated this study using baboons as the experimental animals.[12] Hemoglobin was prepared from outdated blood. The constituents are shown in Table 1. The hemoglobin solution was anemic and the hemoglogin oxygen affinity state was increased as reflected by the reduced P_{50} value. Nine animals underwent total exchange transfusion with hemoglobin solution, and nine control animals underwent exchange transfusion with dextran 70. All animals given hemoglobin solution survived to zero hematocrit. In contrast, all nine control animals died at hematocrit levels of approximately 5%.

The dextran-treated animals responded to isovolemic anemia by an increase in cardiac output, an increase in oxygen extraction, and a decrease in mixed venous oxygen pressure ($P\bar{v}O_2$). The hemoglobin-treated animals developed no changes in oxygen consumption at zero hematocrit when compared with baseline levels, thereby confirming the observations of Mulder et al.[13] The maintenance of normal oxygen consumption at zero hematocrit was achieved solely through the mechanism of increased oxygen extraction leading to low $P\bar{v}O_2$ levels. The fact that oxygen consumption was unchanged at zero hematocrit was remarkable because a radical change in the circulation had occurred. Blood containing 12 grams of hemoglobin per deciliter with a P_{50} of 32 torr was acutely replaced with anemic blood of 7 g/dL with a P_{50} of 12 torr. Also remarkable was the mechanism of maintenance of normal oxygen consumption at zero hematocrit. In view of the profound shift in the affinity state, an increase in cardiac output rather than an elevation in oxygen extraction would have been the expected response.

We were surprised and encouraged that baboons could temporarily survive such a massive assault on their circulation. A number of questions surfaced from this study. One question concerned the dramatic reduction in $P\bar{v}O_2$ to 20 torr in the hemoglobin-treated animals at zero hematocrit. The $P\bar{v}O_2$ is the tension at which oxygen unloads from the hemoglobin and is in equilibrium with the tissue PO_2. Such a low $P\bar{v}O_2$ was alarming and led us to attempt its correction.

NORMALIZATION OF MIXED VENOUS OXYGEN TENSION

Factors that affect $P\bar{v}O_2$ include an increase in oxygen consumption and a decrease in cardiac output, arterial saturation, hemoglobin

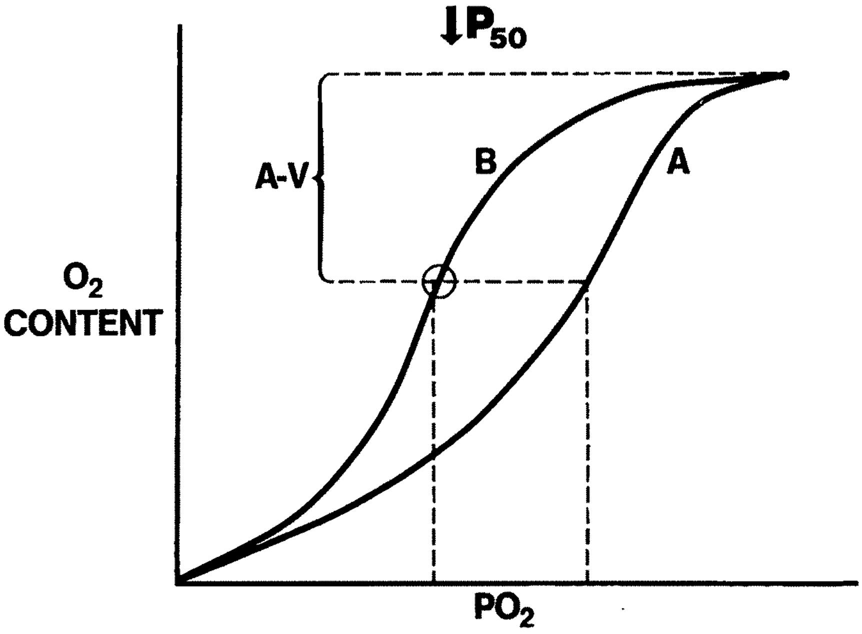

Figure 2. Effect of a leftward shift in the oxygen content curve. Curve A is in the normal position. Curve B is shifted leftward. Assuming no change in A-VDO_2, the result must be a decline in the P$\bar{v}O_2$.

mass, or affinity state. In reviewing our baboon data, we could eliminate changes in oxygen consumption, arterial saturation, and cardiac output as possible explanations for the decline in P$\bar{v}O_2$. That left changes in hemoglobin mass and affinity state for further consideration. We examined affinity state changes first. Figure 2 demonstrates how a leftward shift in the content curve could produce a decrease in the tension at which oxygen unloading occurs—the P$\bar{v}O_2$. This possibility was confirmed by Riggs et al,[16] who exchange transfused monkeys with high-affinity banked monkey blood. They noted no change in cardiac output or arteriovenous oxygen content difference (A-VDO_2). They did observe a significant decrease in P$\bar{v}O_2$. No data existed concerning the consequences of normalizing a leftward-shifted curve.

The increase in affinity state in the hemoglobin solution is related to the loss of the organic ligand 2,3-diphosphoglycerate (2,3-DPG), normally found within the red blood cell. Attempts to normalize P_{50} by the addition of 2,3-DPG to the hemoglobin solution itself were unsuccessful because the DPG rapidly disappears from the circulation after infusion.[23] Benesch et al,[1] Greenberg et al,[6] and Sehgal et al[21] described a modification of the hemoglobin molecule by the addition of pyridoxal phosphate. The resulting compound, pyridoxylated hemoglobin, exhibits a P_{50} considerably higher than the P_{50} of unmo-

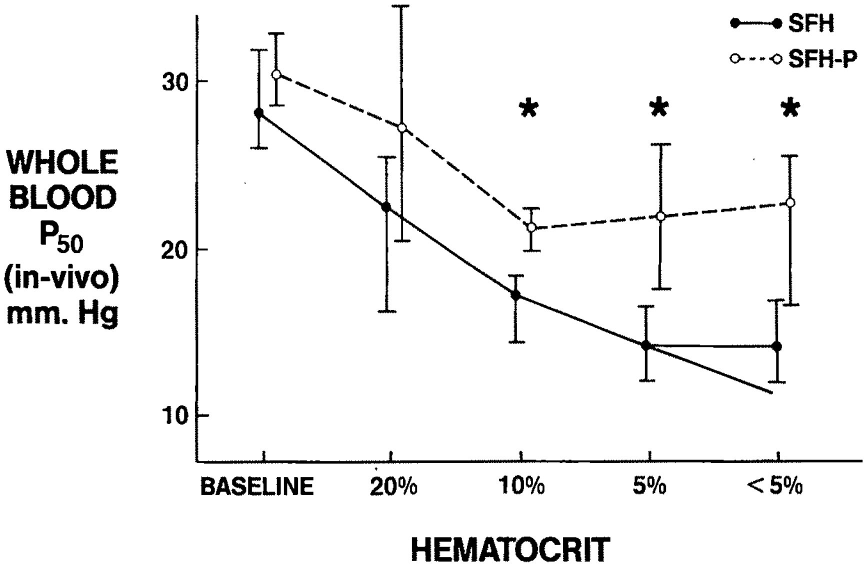

Figure 3. Whole blood in vivo P_{50} versus hematocrit (mean value and range). *Significant difference ($P < 0.05$).

dified hemoglobin. This modification allowed us to examine the $P\bar{v}O_2$ in animals that were exchange transfused with pyridoxylated hemoglobin.[4]

Eight baboons were the test animals. Four received unmodified hemoglobin (P_{50} = 12 torr), while four received pyridoxylated hemoglobin (P_{50} = 22 torr). The exchange transfusion was carried out until zero hematocrit was achieved. The hemoglobin concentration of both solutions was approximately 7 g/dL. No important changes were noted following exchange transfusion in either group in oxygen consumption, cardiac output, or A-VDO_2. Figure 3 demonstrates that animals that underwent exchange transfusion with pyridoxylated hemoglobin developed significantly higher whole blood P_{50} levels compared with those given unmodified hemoglobin when the hematocrit levels declined to 10%. From this point onward, $P\bar{v}O_2$ levels were substantially higher in the animals given pyridoxylated hemoglobin (Fig. 4).

These data illustrate two points. First, they confirm the concept that rightward shifts in the dissociation curve result in an increased $P\bar{v}O_2$, as long as cadiac output and A-VDO_2 remain constant. This is important because it allows for unloading to occur at a higher tissue PO_2. Second, the $P\bar{v}O_2$ level in the animals treated with pyridoxylated hemoglobin was still substantially lower than the 40 to 50 torr found in control animals. Thus, we decided to search for other means to normalize the $P\bar{v}O_2$ in animals that underwent total exchange tranfusion with hemoglobin solution. This led us to examine the quan-

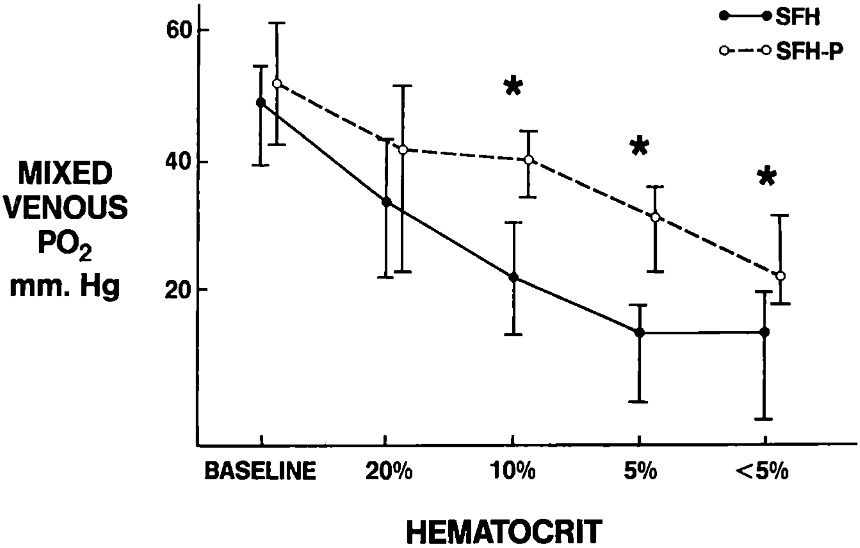

Figure 4. Mixed venous oxygen tension versus hematocrit (mean value and range). *Significant difference ($P < 0.05$).

titative relationship among changes in hemoglobin concentration, P_{50} levels, and $P\bar{v}O_2$.

HEMOGLOBIN CONCENTRATION, P_{50}, AND MIXED VENOUS OXYGEN TENSION

Little information existed concerning the relationship among changes in hemoglobin concentration, P_{50}, and the resultant $P\bar{v}O_2$ in animals receiving hemoglobin solution. Such information might suggest whether we should focus on further efforts to increase the P_{50} of the hemoglobin solution or attempt to increase the hemoglobin concentration.

In this study 15 baboons underwent total exchange transfusion with pyridoxylated hemoglobin with a P_{50} of 21 torr and a hemoglobin concentration of 7 g/dL.[5] The result involved simultaneous changes in both the recipient hemoglobin concentration and P_{50}. To assess the effect of each of these two variables on $P\bar{v}O_2$, we used a multiple linear regression model. The equation was as follows:

$$\Delta P\bar{v}O_2 = a\Delta[Hb] + b \cdot \Delta P_{50} \qquad (1)$$

where a is the coefficient for hemoglobin concentration and b is the coefficient for P_{50}. The results are shown in Table 2. The important results are a decrease in hemoglobin concentration of 6.5 g/dL and a

Table 2. *Pre-Exchange and Post-Exchange Oxygen Transport Variables*

VARIABLE	BASELINE	AFTER EXCHANGE
$P\bar{v}O_2$ (torr)	51.4 ± 1.5	22.4 ± 2.6*
Hemoglobin concentration (g/dL)	11.6 ± 0.3	5.1 ± 0.4*
P_{50} (torr)	31.0 ± 0.9	19.5 ± 1.6*
Oxygen consumption (cc/min/kg)	4.5 ± 0.3	3.2 ± 0.3*
Cardiac output (L/min)	3.3 ± 0.2	2.8 ± 0.2
Oxygen saturation	0.96 ± 0.003	0.96 ± 0.007

Mean ± SE.

* Significantly different from baseline ($P < 0.001$).

decrease in P_{50} of 21.5 torr. These changes were associated with a decline in $P\bar{v}O_2$ of 29 torr.

The coefficients of each variable (calculated from the equation) and contributions of each variable to the change in $P\bar{v}O_2$ are shown in Table 3. The results show that the 6.5-g/dL decrease in hemoglobin concentration produced a 26 torr decline in $P\bar{v}O_2$, whereas an 11.5 torr decline in P_{50} produced only a 3.8-torr decrease in $P\bar{v}O_2$. These changes clearly indicate that further efforts should be directed toward normalizing the hemoglobin concentration.

NONANEMIC ISO-ONCOTIC HEMOGLOBIN SOLUTION

The advantges of a nonanemic hemoglobin solution are self-evident. Such a solution would have the same oxygen capacity as whole blood. In addition, according to our data, the infusion of a nonanemic solution should be associated with normal $P\bar{v}O_2$ levels, even at zero hematocrit. The principal obstacle to normalization of hemoglobin concentration is the effect of an elevation in protein concentration on oncotic pressure.

The relationship between hemoglobin concentration and oncotic pressure is shown in Figure 5.[18] At hemoglobin concentrations of 7 g/dL, the oncotic pressure is similar to that of plasma—20 torr. In

Table 3. *Calculated Changes in Mixed Venous Oxygen Tension**

VARIABLE	AVERAGE TOTAL CHANGE (Δ)	MULTIPLE REGRESSION COEFFICIENT	CONTRIBUTION TO Δ $P\bar{v}O_2$ (TORR)
Hemoglobin concentration (g/dL)	−6.5	4.0	−26.0
P_{50} (torr)	−11.5	0.33	−3.8
		Total calculated Δ $P\bar{v}O_2$ versus	−29.8
		observed Δ $P\bar{v}O_2$	−29.0

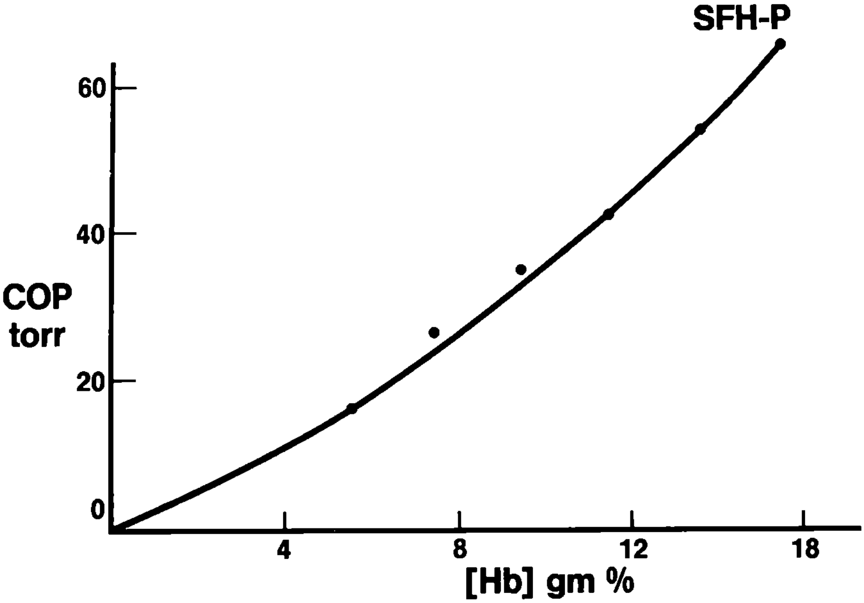

Figure 5. Relationship between colloid osmotic pressure (COP) and hemoglobin concentration ([Hb]) for polymerized stroma-free hemoglobin (SFH-P).

contrast, at hemoglobin levels of 15 g/dL, oncotic pressure increases by more than 300%. The infusion of such a solution would theoretically produce large shifts of fluid from the extravascular space into the intravascular space. These changes are likely to be exceedingly harmful.

One approach to producing a nonanemic hemoglobin solution with normal colloid osmotic pressure (COP) values is polymerization of the hemoglobin. The COP of any solution is proportional to the number of colloidal particles. If a 15-g/dL solution of hemoglobin could be polymerized, the result would be a reduction in COP, whereas no change would occur in hemoglobin concentration (Fig. 6).

This idea was tested in our laboratories.[19] Approximately 14 L of the hemoglobin solution thus obtained is pyrixdoxylated by modification of previously described techniques.[1,6] Briefly, pyridoxal-5′-phosphate is added to the solution on a 4:1 molar ratio. The solution is transferred to a 20-L sealed reservoir (Millipore Corp., Bedford, MA) and deoxygenated with N_2 using a gas exchanger (William Harvey Co., Santa Ana, CA). De-oxygenation of the solution is continued until the P_{O_2} is below 10 torr and the oxygen content is below 1 vol%.[19] Sodium borohydride is then added to the solution and the reaction continued for 2 to 4 hours.

The goal of the polymerization is to normalize the O_2 capacity while maintaining the COP within normal limits (20 to 25 torr). There are several parameters that one can manipulate in order to obtain, in

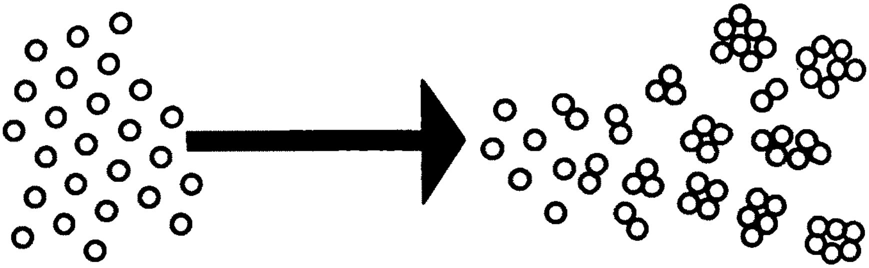

Figure 6. Polymerization results in a reduction in colloid osmotic pressure (COP) while maintaining a constant hemoglobin concentration ([Hb]). [Hb]-15 g/dL [Hb]-15 g/dL COP > 70 torr → COP = 25 torr.

a reproducible manner, the polymerized solution of choice.[24] These are the hemoglobin concentration, the concentration of the polymerizing agent, the rate of addition of the latter, and the rate of mixing. Finally, the duration for which the above parameters are controlled will, in turn, determine the reaction yield, molecular weight distribution of the polymeric species, oxygen affinity (P_{50}), and finally, the viscosity of the solution.

The details of the polymerization have been previously described.[20] The polymerization is conducted to a physiologic endpoint with respect to COP. The reaction is thus monitored by the decrease in COP. Figure 7 shows the changes in COP monitored during the polymerization process conducted over a 3-hour period. As can be seen from the figure, the reproducibility of the process over five batches is quite acceptable.

The polymerization and the evolution of the polymeric species is also followed by SDS-PAGE. Figure 8 shows the formation of new polypeptide bands over the duration of the process. Typically, 4 to 6 bands are seen, ranging in molecular weights from 16,000 to 96,000 daltons. The first 4 bands (16,000 to 64,000 daltons) represent greater than 90% of all species.

With the formation of polymers, one would expect changes in the viscosity of the solution. Figure 9 shows changes in viscosity observed over five different batches. The viscosity at the start of polymerization ranges from 1.0 to 1.5 cp and increases to reach a range of 1.9 to 2.1 cp at the end. This represents a relatively modest increase, but is consistent with the absence of large molecular weight species in the solution, as demonstrated by SDS-PAGE.

The changes in P_{50} during the polymerization were followed and are shown in Figure 10. One notes a modest increase in P_{50} in all five batches shown. This increase reflects a decrease in buffering capacity of the solution with polymerization. It is consistent with the observation that a drop in pH is observed during the course of the polymerization. This is not surprising because it is some of the same amino groups that are involved in the buffering as well as the cross linking.

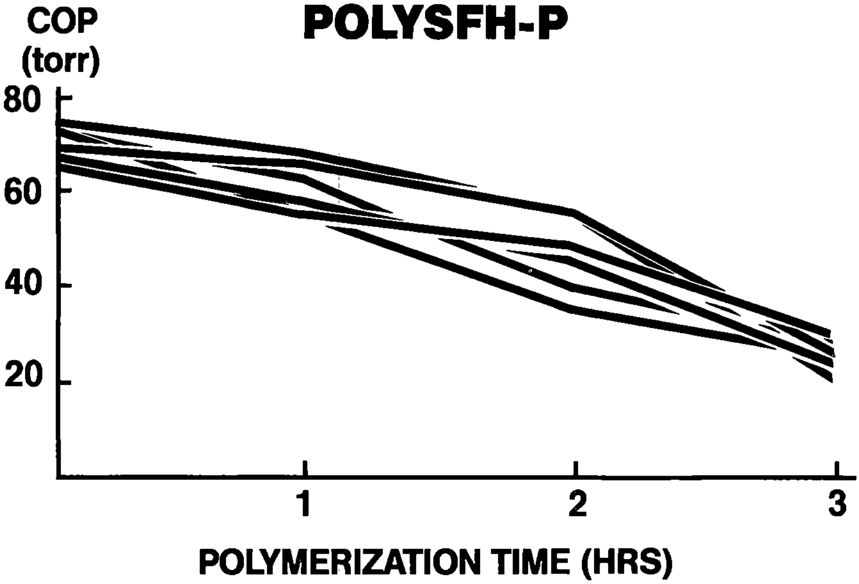

Figure 7. The figure shows the decrease in COP measured during the course of polymerization for five different batches.

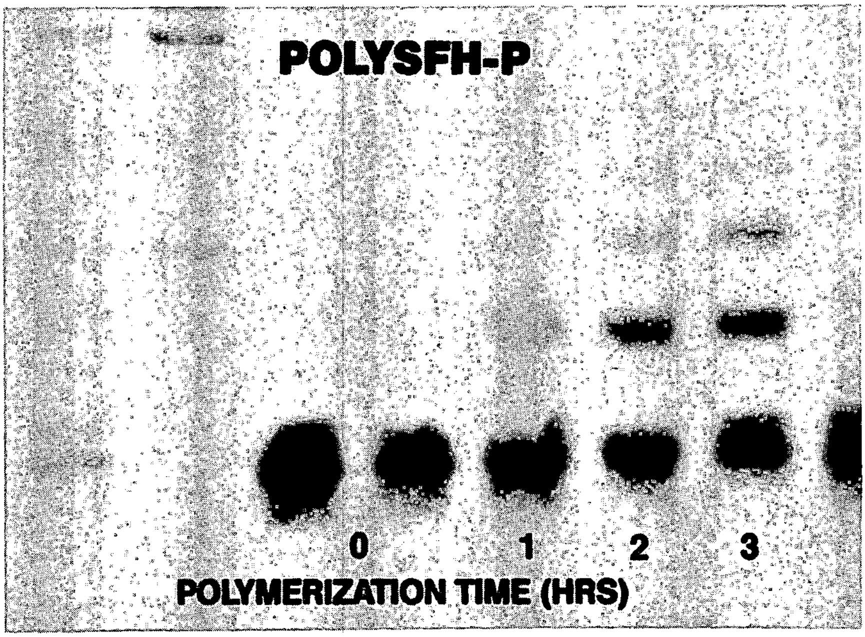

Figure 8. The figure shows the evolution of new polypeptide bands over the course of the polymerization process, as monitored by SDS-PAGE.

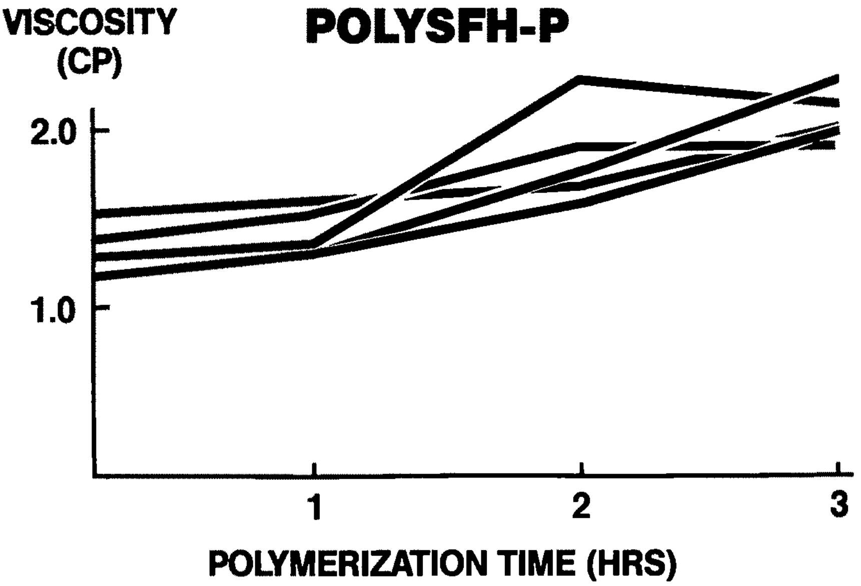

Figure 9. The figure shows the changes in viscosity of five batches of hemoglobin solution during polymerization.

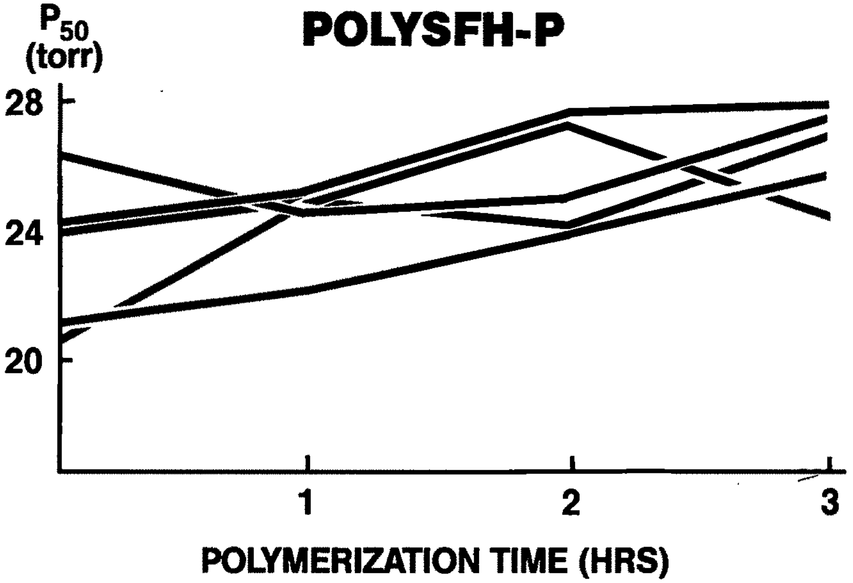

Figure 10. The figure demonstrates the alteration in P_{50} for five different batches of hemoglobin solution during polymerization.

Table 4.

Hemoglobin	12–14 g/dL
Methemoglobin	<5%
Molecular weight range	64–400 × 10 daltons
M_n	150,000 daltons
P_{50}	18–22 torr
Binding coefficient	1.30 cc O_2/g Hb
Hill coefficient	1.5–2.0
Bohr coefficient	−0.12 to −0.25
COP	20–25 torr
Viscosity	1.9–2.2 cp
Phospholipids	<0.4 mg/dL
Limulus amebocyte lysate assay	<0.625 EU/mL
Rabbit pyrogen test	Pass

The characteristics of the final product are listed in Table 4. The solution at 12 to 15 g/dL has a COP between 20 to 25 torr. The molecular weight range based on SDS-PAGE and high-pressure liquid chromatography (HPLC) is between 16,000 to 96,000 daltons. The number average molecular weight (M_n) calculated from the COP is 150,000 daltons. The weight average molecular weight (M_w) obtained by ultracentrifugation is 120,000 daltons. The P_{50} of the solution under standard conditions (pH = 7.40, P_{CO_2} = 35 torr, temperature = 35°C)

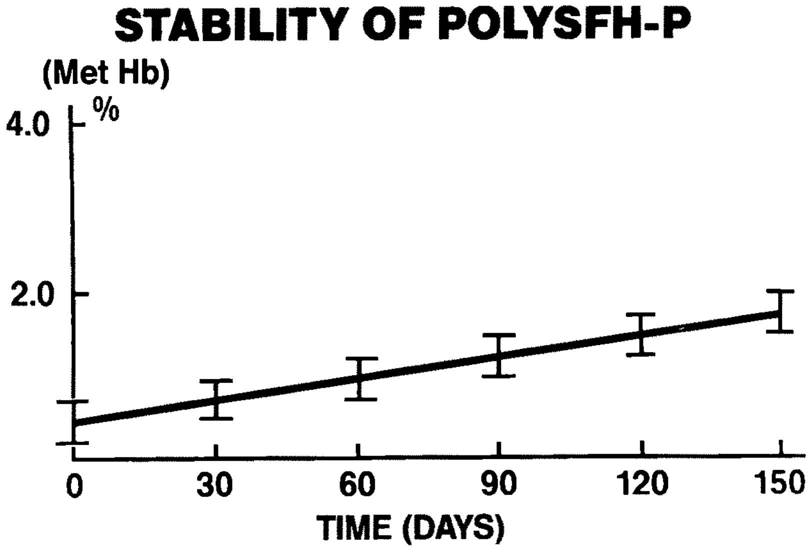

Figure 11. The figure illustrates the changes in methemoglobin concentration upon storage at 4°C to 8°C, as a sterile, pyrogen-free solution. Each point represents mean

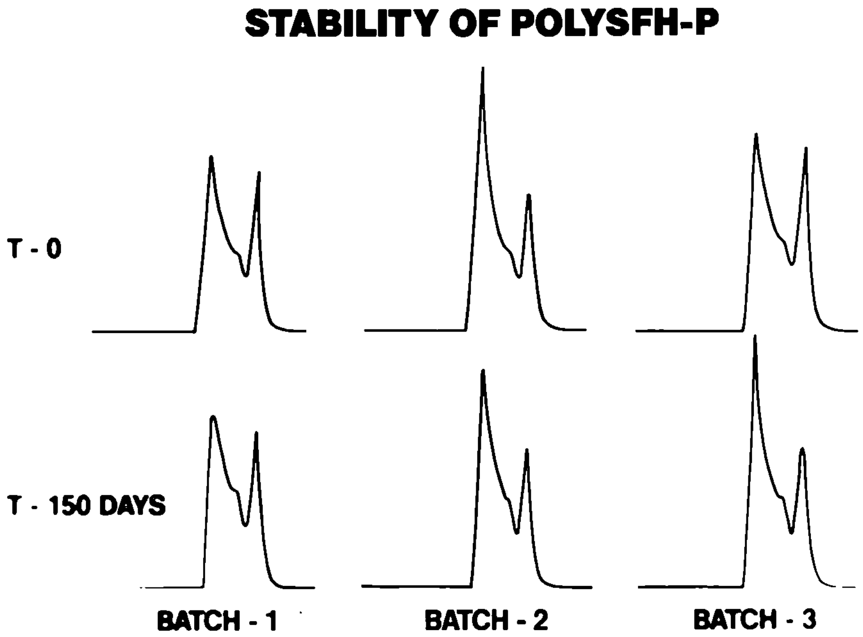

Figure 12. The figure displays the HPLC scans for three batches at the time of manufacture and 150 days later. No changes are noted.

ranges from 18 to 22 torr. The viscosity of the solution ([Hb] = 8.0 g/dL) ranges from 1.9 to 2.2 cp. The phospholipid content is below the detection limits of the thin-layer chromatography technique used (<0.4 mg/dL).

We have followed the stability of the polymerized solution when stored at 4°C to 8°C as a sterile, pyrogen-free product. The stability with respect to rate of conversion to methemoglobin is shown in Figure 11. The methemoglobin remains below 2% for a 150-day period.

The stability of the polymeric species was determined by monitoring the solution by HPLC, SDS-PAGE, and viscosity. No changes were observed over at least a 1-year period. Figure 12 shows the HPLC scans for three different batches at the time of manufacture and 150 days later. No visible changes occurred. Finally, Figure 13 shows the changes in viscosity over a 150-day storage period. Once again, no change in viscosity is seen. Thus, the polymerized stroma-free hemoglobin (Poly SFH-P), when stored at 4°C to 8°C, appears to be very stable.

EFFICACY OF POLY SFH-P

Seven adult baboons were anesthetized, paralyzed, intubated, and mechanically ventilated on room air. The respiratory rate and tidal

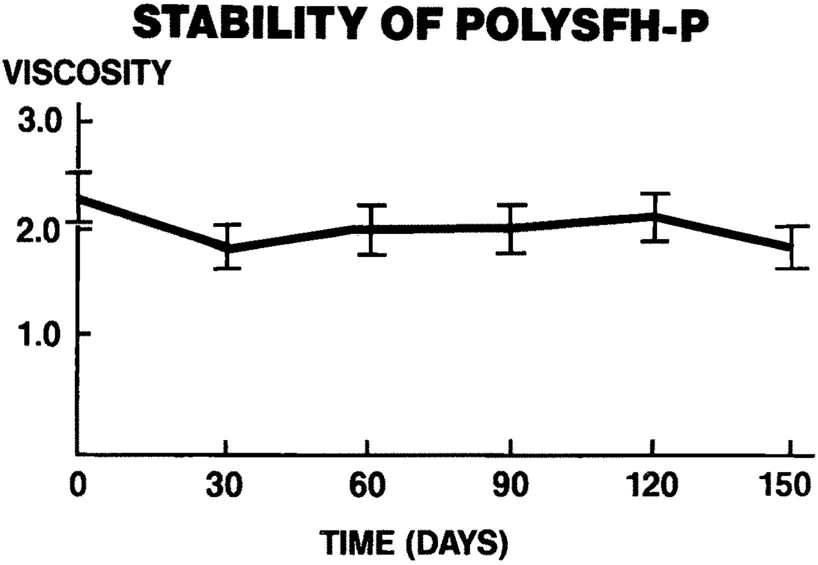

Figure 13. The figure plots the changes in viscosity of five batches, observed over a 150-day period. Each point represents the mean ± SE. No changes in viscosity are observed.

volume were adjusted to maintain a $Paco_2$ between 35 and 45 torr before the start of the study and were not changed during the study. The animals were surgically prepared with arterial and central venous catheters for infusion, blood sampling, and monitoring. A thermal dilution balloon-tipped catheter was floated into the pulmonary artery. A Foley catheter was inserted into the urinary bladder. Standard hemodynamic monitoring was performed for electrocardiogram, arterial pressures, pulmonary capillary wedge pressure, and central venous pressures. Cardiac output was determined by the thermal dilution method.

The study was conducted under ketamine anesthesia. After stabilization of the animals, a set of baseline measurements was obtained. An isovolemic exchange transfusion with the Poly SFH-P was then performed. Whole blood was removed in 50-mL aliquots, and was replaced with approximately equal volumes of the infusate. Additional volume adjustments were made as required to maintain the pulmonary capillary wedge pressure at baseline values. The exchange was stopped at hematocrits of 20%, 10%, and 5% to obtain additional sets of measurements. The exchange transfusion was then carried out to obtain a complete washout of the red cells. A hematocrit of less than 1% was achieved.

These animals, at zero hematocrit, had a Poly SFH-P concentration of approximately 10 g/dL. They were then exchange transfused with dextran 70 to a hemoglobin concentration of 1 g/dL. The data from the second half of the study were compared with a control group (n = 6) that underwent an exchange transfusion with dextran 70 to a hemoglobin concentration of 1 g/dL.

Arterial and mixed venous blood gases were measured by standard electrodes [IL-813]. Whole blood and plasma hemoglobin levels were determined on the IL-282 Co-oximeter.[25] Oxygen carried by whole blood hemoglobin was measured by the IL-282 Co-oximeter. The physically dissolved oxygen in the aqueous phase was calculated from the Po_2 of the plasma separated by centrifugation. The Poly SFH-P O_2 content was measured by the IL-282 Co-oximeter (Instrumentation Laboratory, Lexington, MA). Hematocrits were determined by the microhematocrit method. P_{50} values of whole blood and plasma hemoglobin were determined with the hemoglobin O_2 dissociation curve analyzer (Hem-O-Scan).[26]

The efficacy of the Poly SFH-P was calculated as we have previously described.[27] At each hematocrit level, the O_2 content was determined for each compartment by direct measurement or calculation. Total O_2 delivery was calculated as the product of the cardiac output and the total arteriovenous O_2 content difference [A-VDo_2]. The contribution of Poly SFH-P to O_2 delivery was calculated as the ratio of the Poly SFH-P to total arterial O_2 content (equation 2).[5]

$$\text{Poly SFH-P } O_2 \text{ Delivery} = \frac{[O_2]_{a'}, \text{ Poly SFH-P}}{[O_2]_{a'}, \text{ Total}} \tag{2}$$

The contribution of Poly SFH-P to O_2 consumption was calculated as the ratio of Poly SFH-P to total A-VDo_2.

$$\text{Poly SFH-P } VO_2 = \frac{[\text{A-}VDo_2]\text{Poly SFH-P}}{[\text{A-}VDo_2]\text{Total}} \tag{3}$$

All contributions were expressed as their percent values.

All animals receiving Poly SFH-P survived the exchange transfusion, as did the previous animals receiving SFH-P.[28] The final hematocrit was 0.8 ± 0.4% (mean ± SE). Figure 1 shows the plasma [Hb] values during the exchange. The values with Poly SFH-P at all hematocrits was significant ($P < 0.005$). The difference in the initial bag P_{50} values of the two infusates was statistically significant ($P < 0.05$). However, the mean in vivo plasma P_{50} for the Poly SFH-P was 17.0 ± 0.5 torr, which was not significantly different from the mean value of 17.6 ± 0.8 torr for the SFH-P. Both of these plasma P_{50} values are significantly below the mean baboon red-cell P_{50} of 31.3 ± 0.8 torr. The Poly SFH-P $[O_2]_{a'}$ is significantly greater than the SFH-P value at all hematocrits ($P < 0.001$). At a hematocrit of 5% the $(O_2)_{a'}$ was 9.5 ± 0.2 vol% for Poly SFH-P, and 5.0 ± 0.4 vol% for SFH-P. The percent contributions of Poly SFH-P to total O_2 delivery and total O_2 consumption are shown in Figures 6 and 7. Poly SFH-P makes a significantly greater ($P < 0.02$) contribution to total O_2 delivery than SFH-P at all hematocrits. The contribution to total O_2 consumption is greater by Poly SFH-P at all hematocrits, with the difference significant ($P < 0.005$) at a hematocrit of 20%.

The in vivo P_{50} in the Poly SFH-P animals undergoing the second exchange transfusion with dextran 70 ranged from 18 to 11 torr.[29] In contrast, the in vivo P_{50} of the control group ranged from 31.5 to 25.5 torr. The $P\bar{v}O_2$ was significantly lower in the Poly SFH-P group compared with the control group. Both groups of animals raised their cardiac output in an identical manner in response to their anemia. The critical O_2 delivery in the control group was 6.6 mL/min·kg body weight compared with 5.7 mL/min·kg.

SAFETY OF POLY SFH-P

So far we have discussed the efficacy of hemoglobin solution with regard to oxygen dynamic properties. The next issue is safety. Our concern lies in two areas—nephrotoxicity and immunocompetence.

Nephrotoxicity was reported in early studies following the infusion of hemoglobin solution.[7] Further investigation suggested that the stroma was the toxic factor, probably on the basis of thrombosis of the small renal vasculature.[14] In 1967 Rabiner et al[15] reported that hemoglobin solution, relatively free of stroma, produced no deterioration in renal function following infusion in dogs. These findings were subsequently confirmed in monkeys, even in stressful circumstances of dehydration and shock.[2]

In 1977 Savitsky et al[17] reported the results of a clinical safety trial in humans using stroma-free hemoglobin. Eight healthy male volunteers received a 250-mL infusion of stroma-free hemoglobin at a rate of 2 to 4 mL/min. The hemoglobin concentration of this solution was 6.4 g/dL. The P_{50} was not reported. Two control patients received similar infusions of 5% albumin.

The most striking finding of this study was a decline in creatinine clearance in the hemoglobin solution recipients from a baseline value of 148 to 73 mL/min 1 hour after infusion. This value returned to normal in the second hour following infusion. This alteration in kidney function was accompanied by a sharp decline in urine volume in these patients. In the albumin control patients, no changes were seen in urine volume or creatinine clearance. The authors stressed that this deterioration in kidney function was transient and not associated with permanent renal damage. Nevertheless, these results had a chilling effect on further clinical research.

As Savitsky et al[17] pointed out, there are three possible explanations for the observed nephrotoxicity. The first is stromal toxicity. They did report a stroma lipid level of 1.6 mg/dL. Because this represents only 1% of the original level of phospholipid and the infusion of hemoglobin solution did not produce detectable disseminated intravascular coagulation in the recipients, stromal toxicity is an unlikely explanation.

A second possibility is the presence of a vasoactive substance in the hemoglobin solution that affects renal blood flow. This is supported by the observation that recipients developed transient bradycardia and mild hypertension during the infusion. We noted similar findings in our early hemoglobin solution studies in baboons. We therefore believe that prospective hemoglobin solutions should be tested for the presence of vasoactive substances by bioassay techniques prior to clinical testing.

A third possibility is that the changes in renal function were simply related to the filtration of free hemoglobin through the kidneys. Perhaps hemoglobin filtration in some way interferes with normal kidney function. Once the hemoglobinemia disappears, renal function returns to normal. This is an interesting argument, because the highest level of plasma hemoglobin in the human volunteers was only 57 mg/dL. In actual clinical practice, we expect plasma hemoglobin levels to rise to 6 to 8 g/dL, a thousandfold increase over the levels seen in the clinical safety trials. It is likely that elevations of plasma hemoglobin of that magnitude would produce even greater changes in renal function, especially in a setting of hemorrhagic shock.

In this regard polyhemoglobin has theoretic appeal. The large molecular size of a polymer should rule out renal excretion. The principal route of excretion is presumably the reticuloendothelial system. Thus, nephrotoxicity is less likely with a polymer than it is with the hemoglobin tetramer.

Our second concern is postinfusion immunosuppression. Because sepsis is one of the most serious complications that might develop in circumstances in which hemoglobin solution would be used, it is important to establish that the infusion of hemoglobin solution not impair the host defense mechanism.

The effect of hemoglobin solution on granulocyte function was studied by Hau and Simmons.[8] They showed that hemoglobin acted as an adjuvant in experimental peritonitis in rats by interfering with granulocyte phagocytosis and bacterial killing capability. However, the significance of this finding is not clear, because the hemoglobin only acted as an adjuvant when it was injected into the peritoneal cavity. It was not effective when it was injected intravenously or intramuscularly. In another report, Hoyt et al[9] studied the ability of rats to withstand peritonitis following exposure to hemoglobin solution used as a volume expander in the treatment of hemorrhagic shock. They found no evidence that hemoglobin solution depressed host defense mechanisms.

Whether polyhemoglobin alters immunocompetence is unknown. It is known that the infusion of colloid particles produces blockage of the reticuloendothelial system and thereby enhanced susceptibility to bacterial toxins.[11] Stein and Saba[22] have shown that the infusion of colloid particles not only blocks the reticuloendothelial system but also produces an acute depletion of plasma fibronectin levels. Thus, studies designed to investigate the effects of polyhemoglobin on immunocompetence would be necessary prior to clinical trials.

The solution passes the rabbit pyrogen test, and from batch to batch has between 0.3125 and 0.625 EU/mL as determined by the limulus amebocyte lysate (LAL) assay. In addition, the solution passes the United States Pharmacopeia (USP) safety test, the USP systemic toxicity test, and shows no pressor effects as measured by the USP pressor test.

In addition to these standard tests, baboons receiving Poly SFH-P from 1 to 8 g/kg body weight have been followed for a period of 3 to 6 months, with no alteration in renal function, blood chemistry, and coagulation profile.

On the basis of all the data on safety and efficacy, a further modification of the product was made, leading to the approval to initiate clinical trials on humans. Preliminary results from the trials confirm the preclinical data.[12]

SUMMARY AND CONCLUSION

Attempts to develop a hemoglobin-based red-cell substitute have spanned many decades[12,13] but have not yet resulted in a clinically useful product. The issues that have prevented clinical application have been primarily ones of safety and not efficacy.[27] Numerous animal studies have documented the efficacy of stroma free hemoglobin.[3,12] Though effective, there were limitations that were of concern. Oncotic considerations limit the concentration of the infusate SFH to 6 to 8 g/dL, or half-normal. Owing to the loss of organic phosphate modulators of P_{50} such as 2,3-DPG, the P_{50} of SFH is typically between 12 to 14 torr, which again is half the normal value. And finally, the intravascular half-life of SFH is too short, ranging from 2 to 6 hours.[3]

Polymerization provides a means of correcting these limitations of SFH. The high O_2 affinity can be greatly diminished by covalent binding of pyridoxal-5′-phosphate to the N-terminal of the β-chains. COP exerted by a protein solution is proportional to the number of discrete colloid particles. By polymerization, the number of colloid particles are reduced, leading to a decrease in COP. Our data show that this can indeed be achieved in a reproducible fashion. The rate at which this diminution of COP is accomplished determines the yield of polymeric species, as well as their molecular weight distribution. We demonstrate that the polymerization can be reproducibly controlled to result in a yield of 75% to 85% polymers, with a molecular weight distribution of 128,000 to 400,000 daltons. The number average and the weight average molecular weights indicate that the large proportion of the polymers represent the crosslinking of two tetramers.

The data that reflect the interaction of O_2 with Poly SFH-P indicate that the O_2-carrying function of hemoglobin has not been significantly altered by the chemical modifications. The binding coefficient of O_2 is unchanged. As one would have anticipated, there is a loss of cooperativity (diminished Hill coefficient) between the hemoglobin chains, suggesting structural restrictions in the polymeric species owing to the crosslinking. One would expect to see a reduced alkaline Bohr effect, and our data confirm that. And finally, one would expect to see some increase in O_2 affinity with polymerization. This is indeed the case, though the P_{50} of Poly SFH-P is comparable to banked blood (18 to 22 torr).

A modified hemoglobin solution, to be clinically useful, would need to have a reasonable shelf-life. Our data demonstrate that polymerized hemoglobin can be stored in the cold (4°C to 8°C) for several months with minimum change in methemoglobin concentration. Furthermore, our HPLC and viscosity data clearly indicate that no significant alterations in the polymeric species occur during storage.

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The Approach to the Jehovah's Witness Patient

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One of the more challenging ethical and medicolegal issues that many physicians face is caring for the patient who refuses specific therapeutic interventions based on religious or social dogma. Nowhere is this more demonstrable than in the refusal of blood transfusion by the Jehovah's Witness patient. Based on a strict fundamentalist ideology, members of the Jehovah's Witness sect believe that any intake of blood, or blood products, will jeopardize not only their soul on Earth but also their obtaining eternal life after death. Therefore, they steadfastly refuse even potentially life-saving transfusion for not only themselves, but for their children as well. It is readily apparent that this religious belief may pit physicians and their Hippocratic Oath against Jehovah's Witnesses and their apparent First Amendment right to religious freedom. Thus, a potentially ethical, moral, and legal dilemma may exist for anesthesiologists who, by the nature of their specialty, are at the forefront of managing transfusion therapy.

UNDERSTANDING THE RELIGIOUS BELIEFS OF THE JEHOVAH'S WITNESS

> So then, my beloved brethren, become ye steadfast, immovable, superabounding in the work of the Lord at all times, knowing that your toil is not in vain in the Lord.
>
> (I Corinthians 15:58)

Jehovah's Witnesses are a fundamentalist Christian sect who believe that the Bible is the absolute word of God. The order was originally the offspring of an early 1870s Pennsylvanian Bible study group founded by the self-proclaimed minister, Charles Taze Russell.[21]

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Called "Russellism" and "Millennial Darwinism," the group subsequently became known in the early 1880s as "The Watch Tower Bible and Tract Society." Through distribution of the pamphlet, "Zion's Watch Tower," the society was able to promulgate its religious doctrine so much that by 1909 it was an international organization with headquarters located in Brooklyn, New York. A slight discrepancy exists in the medical literature as to the year its membership became known as "Jehovah's Witnesses."[43, 52] It is clear, however, from the charters of the organization that the present name was affirmed in 1931 by Russell's successor, Joseph F. Rutherford,[56] who adopted it from the following biblical passage:

> Ye are my witnesses saith the Lord [Jehovah], and my servant whom I have chosen.
>
> (Isaiah 43:10)

Despite the fact that this Biblical reference to "witnesses" does not distinguish between Jew and Gentile, Jehovah's Witnesses view Jesus as their Lord's ultimate witness:

> Wherefore, seeing we also are compassed about with so great a cloud of witnesses, let us lay aside every weight, and the sin which doth so easily beset us, and let us run with patience the race that is set before us, looking unto Jesus the author and finisher of our faith.
>
> (Hebrews 12:1,2)

The sect evolved into an energetic and devout congregation, proselytizing openly in an attempt to gain converts to their religious belief that the guidelines God intended to be followed by all human beings can be gleaned from the literal interpretation of the Bible.

Members of the sect refused to recognize any secular authority, assured that only in Jehovah's eyes could they be held accountable. Failure to recognize the offices of government and refusal to offer pledges of allegiance or to enter into military service led to extremes of persecution, including lynching. Prosecution of Jehovah's Witnesses who refused to salute the American flag led to two 1940s Supreme Court rulings ultimately in favor of the Jehovah's Witnesses and what was considered their religious freedom.[40, 57] Jehovah's Witnesses, however, are in no way considered non–law-abiding or militant in their pursuit to disseminate their beliefs. Their strict adherence to Biblical proscriptions is based on a belief that salvation is dependent on remaining faithful to the word of Jehovah. They believe that a Judgment Day will come and only those witnesses who have been sin-free will be granted eternal life. (The final Armageddon is no longer predicted by the sect,[56] despite published reports having stated the contrary.[9])

Presently, Jehovah's Witnesses number more than 3.7 million and are represented in 212 countries, with approximately 800,000 in the United States alone.[60] Their headquarters remain in Brooklyn, New York, and their official journal is still *The Watchtower.*

THE JEHOVAH'S WITNESS AND BLOOD TRANSFUSION

Even if one is not familiar with all of the tenets of this religion, almost all physicians realize that Jehovah's Witnesses do not accept blood transfusions. Unlike members of the Christian Scientist faith, Jehovah's Witnesses actively seek medical attention when ill. However, based on a multitude of Biblical references, Jehovah's Witnesses adamantly oppose blood transfusion. The first referral to this so-called "blood guilt" appeared in *The Watchtower* on December 15, 1927.[42] It was not until the July 1, 1945 issue appeared, however, that the point was profoundly made that the acceptance of a blood transfusion would result in loss of eternal life[24]:

> Seeing, then, that the Most High and Holy God gave plain instructions as to the deposition of blood, in harmony with his everlasting covenant made with Noah and all his descendants; and seeing that the only use of blood that be authorized in order to furnish life to humankind was the use of it as a propitiation of atonement for sin; and seeing that it was to be done upon his holy altar or at his mercy seat, and not by taking such blood directly into the human body; therefore it behooves all worshippers of Jehovah who seek eternal life in his new world of righteousness to respect the sanctity of blood and to conform themselves to God's righteous rulings concerning this vital matter.

There are many Biblical references upon which Jehovah's Witnesses base this refusal of blood transfusion, beginning with the book of Genesis, as God spoke to Noah after the great flood:

> Every moving thing that liveth shall be meat for you; even as the green herb have I given you all things. But flesh with the life thereof, which is the blood thereof, shall ye not eat.
>
> (Genesis 9:3,4)

Further substantiation of their beliefs is offered in the book of Leviticus as God spoke to Moses:

> Moreover, ye shall eat no manner of blood, whether it be of fowl or of beast in any of your dwellings. Whatsoever soul it be that eatest any manner of blood, even that soul shall be cut off from his people.
>
> (Leviticus 7:26,27)

Similar passages in other sections of Leviticus as well as in the book of Deuteronomy also infer "being cut off" (i.e., loss of eternal life) if one eats blood. (See Leviticus 17:10–15; Deuteronomy 12:23.)

Although eating blood and actually receiving an intravenous (IV) transfusion of blood or blood products may seem to be unrelated, Jehovah's Witnesses are quick to point out that physicians would avoid administering an IV medication to a patient with a known oral allergy to the same drug (i.e., it is not the route that is the question but blood itself).[3] They base this analogy also on Biblical passages that implore Gentiles to "abstain from pollutions of idols, and from fornication, and from things strangled, and from blood." (Acts 15:20,29) Even in an emergency situation, transfusion is prohibited; they base this belief on a passage in the First Book of Samuel where battle-fatigued and starving soldiers of Israel killed livestock:

> . . . and the people did eat them with the blood. Then they told Saul, saying, 'Behold the people sin against the Lord, in that they eat with the blood.'
>
> (I Samuel 14:32,33)

The Jehovah's Witnesses' religious objection to whole blood and packed red blood cell (RBC) transfusion is unequivocal. However, the issues of more modern-day transfusion therapy, transplantation, immunization, and vaccination remain less well defined by church hierarchy.

Considering the aspects of primary component therapy (i.e., white cells, platelets, and plasma), *The Watchtower* states: "We believe that the use of blood as a [life-sustaining] transfusion, or the use of a blood component to accomplish a similar purpose, is obviously in conflict with the Scriptural command to 'abstain . . . from blood.' in (Acts 15:20)."[46] Yet, in a study of a Jehovah's Witness congregation in Denver, Colorado, approximately 12% of the members responding to a questionnaire regarding hypothetical transfusion situations would consider accepting plasma as an alternative to blood transfusion.[16]

The use of autologous transfusion is also thought to be unacceptable by the vast majority of Jehovah's Witnesses who state that despite being one's own blood, reinfusion of blood, once it has left continuity with the body, should be "'poured out on the ground as water' to show that it was for God and not to sustain the life of some earthly creature. (Deuteronomy 12:24). In view of this, how could he allow his blood to be collected in a blood bank for later transfusion into himself or another person?"[46] Individual Jehovah's Witnesses, however, have and may consider autologous blood transfusion based on their own interpretation of these Biblical teachings.[16, 52] Intraoperative use of autotransfusion devices has been employed in caring for Jehovah's Witnesses provided, however, that continuity between the collection site and reinfusion port are intact.[38] Similarly, extracorporeal circulation and hemodialysis have been readily accepted by Jehovah's Witnesses, provided that the machines are primed with a nonblood fluid such as saline or Ringer's lactate solution. Viewed as an extension of the circulatory system, the use of these devices, as well as of autotransfusions, are left to the individual so that, "He can make a decision that will leave him with a clear conscience before God."[46]

Anecdotally, a case report of a Jehovah's Witness accepting an epidural blood patch for a postdural puncture headache has been described. The case report describies the use of IV extension tubes and a series of stopcocks to directly instill 20 mL of the patient's blood into the epidural space without breaking continuity between the IV and the epidural needle.[4] (Withdrawal of blood for sampling purposes only is not objected to by Jehovah's Witnesses, given the fact that the blood is tested and then disposed of properly.)

Immunization and vaccination are also considered to be "gray areas" by *The Watchtower*. Certainly, vaccines that are obtained via the use of recombinant DNA methodology would not pose a problem; however, the choice to accept a serum-derived vaccine is left to the individual member.[46]

Human tissue donation and acceptance of transplanted organs (other than bone marrow), despite seeming to be intuitively taboo and despite being unacceptable to many Jehovah's Witnesses,[9] have also been left to the judgment of individual members. *The Watchtower* stated in 1980 that, "While the Bible specifically forbids consuming blood, there is no biblical command pointedly forbidding the taking in of other human tissue."[47] Jehovah's Witnesses believe that the cells of a transplanted organ are replaced by the patient's own cells and, therefore, organ transplantation is considered acceptable.

In an effort to explain and support their religious beliefs regarding blood transfusion, *The Watchtower* published a pamphlet in 1977 called, "Jehovah's Witnesses and the Question of Blood."[33] This pamphlet is readily available upon request to the Society's Hospital Information Services (25 Columbia Heights, Brooklyn, NY, 11201). The pamphlet painstakingly voices objections based on the inherent medical risks involved in receiving a blood transfusion. Printed prior to the risk of human immunodeficiency virus (HIV) transmission, the pamphlet highlights all other possible risks of blood transfusion in a section entitled, "Blood Transfusions—How Much Actual Danger?" This section implies that if the religious basis is insufficient to support their beliefs, then the risk of transfusion reactions and transmissible diseases certainly, ". . . underscores the reasonableness, even from a medical standpoint, of the position that Jehovah's Witnesses take." However, they state this is not the primary reason for objections. Rather, "The fundamental reason why they [Jehovah's Witnesses] do not accept blood transfusions is because of what the Bible says. Theirs is basically a religious objection, not a medical one."

LEGAL CONSIDERATIONS

Even for those physicians who have a clear understanding of the religious beliefs of the Jehovah's Witness patient, an overwhelming concern to save a life may create an ethical and moral dilemma, causing those involved to seek guidance from the courts. Indeed, many middle-of-the-night court petitions have been filed in an effort to grant conservator status to a hospital administrator, thereby permitting transfusion therapy to a nonconsenting patient. Unfortunately, the higher courts have not been totally consistent in their rulings. This stems from a prohibition against the formation of statute law when it relates to the First Amendment right to freedom of religion. Therefore, the decisions that have been rendered thus far have been based solely on the study of case law. The pages to follow will attempt to review the major court decisions that have influenced transfusion practices of physicians caring for Jehovah's Witness patients.

Competent Adult with No Dependents: Elective Procedure

The absolute right of every individual to freely choose and express his or her religious beliefs so long as the expression of such beliefs does not endanger public health, welfare, or morals is a right guaranteed by the First and Fourteenth Amendments of the United States Constitution. Based on these inherent rights, the court will not likely intervene in an elective procedure for a competent adult without dependents who refuses medical treatment. Jehovah's Witnesses will readily sign waivers releasing the hospital and physicians of liability should an untoward event lead to significant injury or death due to lack of a blood transfusion.[14, 33] These documents are binding in a court of law and, therefore, it seems clear that[34]:

> A physician has no legal duty to proceed against the choice of a competent adult who declines medically indicated treatment, even if that refusal leads to the patient's death. In the absence of some important public interest (and courts have been reluctant to find such interests), the competent patient's choice, foolish as it may seem to some observers, will be respected by the law.

On the contrary, if a Refusal of Transfusion Consent form has been signed, then any forced or surreptitious transfusion, or transfusion performed in an attempt to mitigate the unexpected intraoperative catastrophe, will not only open the physician to the claim of malpractice, but also to the potential criminal charge of battery.[17]

However, the Common Law right to refuse is not absolute, as this right must be balanced against the state's interests. These interests were defined in the case of *Superintendent of Belchertown* v. *Saikewicz* in 1977.[53] In this case, the court upheld the rights of a non-Jehovah's Witness patient to refuse nonemergent medical therapy, but also went on to define those circumstances in which the state's interests might supercede the individual's rights to self-determination. These state interests have subsequently been cited in a number of court decisions and include: (1) preserving life, (2) protecting the interests of third parties, (3) preventing suicide, and (4) maintaining the ethical integrity of the medical profession. An example of such a situation would be the forceable treatment and/or isolation of a patient who posed the threat of spreading a contagious disease. However, in the case of a Jehovah's Witness patient, a court decision overruling the patient's objection to transfusion based on a state interest has been cited only in the setting of an emergency, if the patient is incompetent, when dependents are involved, or if the patient is pregnant or a minor. These cases will be discussed in the following sections.

Competent Adult with No Dependents: Emergency Situation

One of the most commonly cited cases in this regard is the case of In re *Estate of Brooks*.[26] This Illinois Supreme Court ruling involved the overturning of a lower appellate court's decision to transfuse an adult Jehovah's Witness with no dependents (husband and two adult children only) for a life-threatening upper gastrointestinal (GI) hemorrhage. Despite the fact that the transfusions had been completed and the patient successfully treated (therefore, appearing to be a moot case), the higher court reversed the appellate court's decision because, ". . . when the issue presented is of substantial public interest, a well-recognized exception exists to the general rule that a case which has become moot will be dismissed upon appeal." In this case, Mrs. Bernice Brooks was a competent adult Jehovah's Witness suffering from severe peptic ulcer disease. She had been treated by a physician who, over the preceding 2 years, was well aware of her religious objections to blood transfusion therapy. In May 1964, she was hospitalized for a severe upper GI hemorrhage. Both she and her husband had signed the appropriate forms relieving the hospital and physician from all liability that might result from the failure to administer blood transfusions in an emergency situation. Nevertheless, despite the reassurances that there would not be an effort to persuade the patient to accept transfusion, and unbeknownst to the patient and her family, the physician and legal counsel sought and obtained conservator status and the authorization to transfuse Mrs. Brooks when it appeared she was no longer capable of a coherent decision. Compelled by what was felt to be the patient's imminent death, the physician administered whole blood transfusions. (It is of note that this was not without complications as the patient developed "circulatory overload"). In its final analysis, the Supreme Court of Illinois predicated its decision upon a fundamental issue based on the facts of the case:

> When approaching death has so weakened the mental and physical faculties of a theretofore competent adult without minor children that she may properly be said to be incompetent, may she be judicially compelled to accept treatment of a nature which will primarily preserve her life, but which is forbidden by her religious convictions and which she has previously steadfastly refused to accept, knowing death would result from such refusal?

The Supreme Court of Illinois ruled that appointment of conservator status and authorization to transfuse, without notice to her or her family, was in direct violation of the patient's constitutional rights. This decision was based on the following facts: Mrs. Brooks had notified both physican and hospital of her belief that acceptance of a blood transfusion was against her religious principles, that she had signed all appropriate release forms, that no minor children were involved, and that, "there appeared otherwise no clear and present danger to society." Therefore, the lower court's decision was overturned.

In 1971, the Supreme Court of New Jersey, on the contrary, chose to argue in favor of state interests in the case of *John F. Kennedy Memorial Hospital* v. *Heston.*[35] The patient, Delores Heston, was a 22-year-old, unmarried female with no dependents, who presented to the hospital of note after having sustained a ruptured spleen in a motor vehicle accident. The patient and her mother were Jehovah's Witnesses who, upon admission, clearly stated their religious objections to blood transfusions. The patient's mother signed a release of liability form; however, due to her worsening condition, the patient was unable to sign the form. With death appearing to be imminent, and after notification of the patient's mother, the hospital requested and was granted by a superior court conservator status with the authority to initiate blood transfusion. Approximately 3 hours after appointment of the conservator, the patient underwent successful splenectomy in conjunction with whole blood transfusions. The patient survived, but moved to vacate the order authorizing transfusion, stating that her civil rights had been violated. Unlike the Illinois Supreme Court, the New Jersey Supreme Court ruled that no patient has, "a constitutional right to choose to die . . . nor is constitutional right established by adding that one's religious faith ordains his death." Essentially, the higher court upheld the lower court's ruling based on the state's vested interest in preventing suicide and preserving life:

> It is arguably different when an individual, overtaken by illness, decides to let it run a fatal course. But unless the medical option itself is laden with the risk of death or of serious infirmity, the state's interest in sustaining life in such circumstances is hardly distinguishable from its interest in the case of suicide.

Finally, this court also felt that because the hospital and the physicians were involuntary custodians, having had the patient "thrust upon them" (unlike the Brooks case in which the physician was well acquainted with the patient), the state's interest in maintaining the ethical integrity of the medical profession outweighed the patient's religious objections.

Some may argue that this case deals with an incompetent patient. However, there is no question that the patient expressed her convictions while fully lucid, and it was not until she became so ill as to lapse into an unconscious state that the court interceded.[5, 15] One could assume that in an emergency situation of acute hemorrhage, eventually all patients might be judged incompetent. The question raised, therefore, is whether the physician and the court may determine when a competent patient's decision becomes that of an incompetent patient.

It is readily apparent that no clear consensus can be obtained in these matters, and it becomes even more complex when dependents and minors are involved. These cases are discussed in the sections to follow.

Competent Adult with Dependents: Emergency Situation

The first and perhaps most cited and controversial decision involving a court-authorized transfusion in a competent adult with dependents was the case of *Jones* v. *the President and Directors of Georgetown College, Inc.*, in 1964.[30] The patient was a 25-year-old Jehovah's Witness (with a 7-month-old child) who presented with a severe upper GI hemorrhage secondary to peptic ulcer disease. The patient, while awake, alert, fully competent, and in the presence of her husband, refused such therapy. A petition was then filed in a

Washington, D.C., district court on behalf of the hospital to grant authorization for blood transfusion. Having had this motion denied, the representing attorneys approached an appellate court judge, in chambers, asking for a review of the district court's ruling. The appellate judge went to the hospital and spoke with the patient's physician and husband, and finally with the patient herself. Now, extremely weak, she was only able to answer the judge's concern to transfuse by saying, "against my will." The judge later stated that, "It was obvious that the woman was not in a mental condition to make a decision. . . . I asked her whether she would oppose the blood transfusion if the court allowed it. She indicated, as best I could make out, that it would not then be her responsibility." Based on the following arguments, the judge authorized transfusion:

1. The patient was (now) incapable of making a judgment.
2. The state, as *parens patriae*, had an interest in preserving the life of a mother of an infant.
3. The patient wanted to live and it was the feeling of the court that if the law were made responsible for authorizing the transfusion without her consent, then her life would be saved without compromise of religious beliefs.
4. Given the urgency of the situation, refusal to act, only to find later that the law required action, was a risk the court was not willing to accept.

Having been successfully transfused and discharged from the hospital, the patient moved to vacate the order. Her appeal was denied, however, by both the appeals court and, eventually, the US Supreme Court due a procedural technicality. However, of note was an opinion offered by a member of the appeals court, future Chief Justice Warren Burger, who, despite agreeing to deny the petition, recalled the philosophy of another Supreme Court Justice, Louis Brandeis:

> The makers of our constitution . . . sought to protect Americans in their beliefs, their thoughts, their emotions and their sensations. They conferred, as against the Government, the right to be let alone—the most comprehensive of rights and the right valued by civilized man.

Justice Burger went on to state[2]:

> Nothing in this utterance suggests that Justice Brandeis thought an individual possessed these rights only as to sensible beliefs, valid thoughts, reasonable emotions, or well-founded sensations. I suggest he intended to include a great many foolish, unreasonable and even absurd ideas which do not conform, such as refusing medical treatment even at great risk.

In 1965, a federal court in Connecticut ordered that transfusions be administered to a 39-year-old Jehovah's Witness, father of four children, who voluntarily admitted himself to the hospital for treatment of a serious upper GI hemorrhage.[54] The patient and his wife signed release forms relieving the hospital and those caring for the patient from civil liability in the event of injury due to failure to transfuse. The court, upon request from the hospital, intervened and interviewed the patient at the bedside. When the judge approached, the patient's first remarks were:

> . . . that he would not agree to be transfused but would in no way resist a court order permitting it, because it would be the court's will and not his own. His 'conscience was clear' and the responsibility for the act was 'upon the court's conscience.' He stated he would rather die than agree to a transfusion.

Despite the patient's coherent and rational behavior, the court authorized transfusion. Citing *Georgetown*, the court ruled[2]:

> In the difficult realm of religious liberty, it is often assumed only the religious conscience is imperiled. Here, however, the doctor's conscience and professional oaths must also be respected. In the present case the patient voluntarily submitted himself to and insisted upon medical care. Simultaneously he sought to dictate to treating physicians a course of treatment amounting to medical malpractice. To require these doctors to ignore the mandates of their own conscience, even in the name of free religious exercise, cannot be justified under these circumstances. The patient may knowingly decline treatment, but he may not demand mistreatment.

Contrary opinions have also been issued in regard to the competent patient with dependents or the competent patient with dependents who, due to a rapid worsening of the underlying medical condition, becomes incompetent. Such was the case that was decided in 1972 in *Holmes* v. *Silver Cross Hospital of Joliet, Illinois*.[22] This case involved a 24-year-old Jehovah's Witness, father of one child, who presented to the hospital after sustaining serious injuries in a motor vehicle accident. While fully competent, he and his family members informed the physicians of their religious objections to blood transfusion should one be necessary. However, within 4 hours, the patient's condition deteriorated to the level of unconsciousness, at which point the physicians and hospital, without notifying the patient's family, requested and received authorization from a probate court to transfuse. The patient expired despite the transfusion therapy, and his family brought action against the hospital and staff, claiming violation of civil rights. A United States district court concluded that, indeed, the patient's and family's civil rights had been violated and that the family's complaint was valid.

Two other notable cases have also ruled in favor of the Jehovah's Witnesses' right to refuse transfusion. In 1972, in the case of In re *Osborne*, a 34-year-old man with two children presented after sustaining severe crush injuries.[29] Both a lower court and an appellate court in the District of Columbia felt that the patient's children would be well cared for in the event of his death. Finding the patient to be competent and finding no compelling state interest, an order to transfuse was not granted. Finally, in 1987, a Florida court of appeals reversed a lower court's ruling to transfuse a 38-year-old female Jehovah's Witness with two children in *Wons* v. *Public Health Trust of Dade County*.[59] Also noting strong family support, the court declared that the state could not mandate a two-parent versus a one-parent family and, therefore, could not invoke the state's interest in ordering a transfusion.

Incompetent Patient

As already mentioned, defining competency may be the primary issue itself; however, when dealing with the patient who presents already unconscious, case law favors the physician who initiates emergency transfusion.[10, 27] In the case of In re *Estate of Dorone* in 1987, the court granted permission to transfuse a 22-year-old Jehovah's Witness who presented unconscious after sustaining acute subdural hematomas in a motor vehicle accident. The Supreme Court of Pennsylvania reaffirmed a lower court's ruling to transfuse despite the objections of the patient's parents, stating:

> Nothing less than a fully conscious contemporaneous decision by the patient will be sufficient to override evidence of medical necessity. When evidence of this nature is measured against third party speculation as to what an unconscious patient would want there can be no doubt that medical intervention is required.

Even when it appears that family and friends are expressing the wishes of the patient, courts feel that[29]:

> Where the patient is comatose, or suffering impairment of capacity for choice, it may be better to give weight to the known instinct for survival which can, in a critical situation, alter previously held convictions. In such cases it cannot be determined with certainty that a deliberate and intelligent choice has been made.

Pregnancy

In cases involving pregnant Jehovah's Witness patients, the courts have invariably sided with the rights of the fetus, especially in the setting of a mid- to late-term gestation. The most celebrated case (non-Jehovah's Witness) establishing the state's right in protecting the life of an unborn child was that of *Roe* v. *Wade* in 1973.[50] In actuality, 9 years earlier in *Raleigh Fitkin-Paul Morgan Memorial Hospital* v. *Anderson*, the New Jersey Supreme Court ruled in a similar fashion when it reversed the order of a lower court and ordered transfusion therapy, if necessary, for a pregnant Jehovah's Witness at 32 weeks' gestation.[48] Even though the patient discharged herself from the hospital and the case appeared moot, the court rendered a decision in the event, "that the matter would arise again at the instance of an interested party." Their decision stated that in the setting of a life-threatening emergency, the state's interest outweighed the mother's religious objections and entitled the fetus to protection under the law. In a similar case, although apparently involving a non-Jehovah's Witness, the Georgia Supreme Court, in 1981, ordered a patient with complete placenta previa to undergo a cesarean section and receive any needed transfusions despite her religious objections to both surgery and blood products.[32] Finally, in 1985, in the case of *In the matter of the Application of Jamaica Hospital,*[31] a New York court appointed a conservator in order to transfuse a Jehovah's Witness with an 18-week gestation pregnancy in the event that the esophageal varices that she had developed were to hemorrhage, thereby threatening the life of her fetus. Collectively, these decisions are clearly based on the concept that, "Laws are made for the government of actions, and while they cannot interfere with mere religous belief and opinions, they may with practices."[49]

Minors: Emergency Situation

Without question, one of the most emotionally charged issues that physicians deal with occurs when caring for the Jehovah's Witness child who requires, but whose parents refuse, blood transfusion. The teachings of the religion ask the question of whether a physician should feel compelled to transfuse a child, "in spite of the resolute wishes of the parents and perhaps even of the child itself." Their answer is dogmatically expressed by saying that, "in view of the well-recognized right of parental responsibility, the moral, principled and consistent position for a doctor is to recognize the responsibility of loving, concerned parents to make decisions for their minor children."[33] Despite offering up support for their beliefs in both the medical and legal literature, case law, without exception, favors transfusing the Jehovah's Witness minor in an emergency situation. The first and most cited case was *Wallace* v. *Labrenz* in 1952.[55] This case involved an 8-day-old infant girl who was diagnosed with erythroblastosis fetales. Expert testimony of three physicians stated that the child would die, or at best suffer permanent brain damage, unless immediate blood transfusion was performed. When the parents refused to consent to this, a petition was filed in a circuit court requesting conservator status for the hospital so as to authorize transfusion. The court acknowledged the parents' loving concern for their child; however, it ruled that their refusal to consent to transfusion represented "neglect" and ordered that custody of the child be granted to a court-appointed guardian for the sole purpose of authorizing an expeditious transfusion. This was performed and the child's health improved. Appeals were filed by the family and, although being a moot case, the Illinois Supreme Court rendered a decision reaffirming the lower court's ruling of neglect. In so doing, they stated: "We entertain no doubt that this child, whose parents were deliberately depriving it of life or subjecting it to permanent mental impairment, was a neglected child within the meaning of the statute." This special form of neglect, coupled with the state's doctrine of *parens patriae*, has enabled the courts to authorize a transfusion for a minor when it is evident that an emergency exists. Finally, the court went on to cite a 1944 US Supreme Court decision prohibiting a Jehovah's Witness from having their child distribute religious pamphlets, declaring[45]:

> The right to practice religion freely does not include liberty to expose the community or child to communicable disease or the

> latter to ill health or death. . . . Parents may be free to become martyrs themselves, but it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves.

Minors: Elective Situation

Unlike the competent adult who refuses elective therapy, the courts as *parens patriae* have intervened in order to transfuse a Jehovah's Witness minor even in an elective, non–life-threatening situation. This was indeed the case in 1970 in In re *Sampson.*[51] The patient was a 15-year-old son of a Jehovah's Witness who suffered from severe facial disfigurement secondary to neurofibromatosis. While the boy's life was in no apparent danger, the Family Court and, subsequently, the New York Court of Appeals ruled that surgery was to be performed to correct the deformity, with transfusions administered, if necessary. They concluded that the state's paramount duty was to insure this child the right to develop without deformity and to guarantee him the right to live and grow up with a sound mind and body. This decision was made despite the parent's religious objection.

In 1972, however, the Supreme Court of Pennsylvania ruled in the opposite manner in the similar case of In re *Green.*[28] In this case, the patient was a 16-year-old son of a Jehovah's Witness with severe scoliosis secondary to poliomyelitis. Despite having a deformity that would eventually lead to the patient being permanently bedridden, the court stated it would not order the child to undergo spinal fusion. Disagreeing with the ruling in *Sampson*, and viewing the problems created by *Sampson* to be "endless," the court went on to stipulate that,

> We are of the opinion that as between a parent and the State, the State does not have an interest of sufficient magnitude outweighing a parent's religious beliefs when the child's life is not immediately imperiled by his physical condition.

Finally, a more recent 1989 Illinois Supreme Court ruling in the case In re *E.G.*[25] addresses the issue of when a minor is mature enough to make his or her own decision regarding medical treatment. In this case, a 17-year-old daughter of a Jehovah's Witness was diagnosed with acute non-lymphocytic leukemia. Both the patient and her mother refused transfusion as part of the therapy required to achieve remission. On the grounds that E.G. was a neglected minor, a lower court granted the hospital's request for a temporary guardian and transfusion therapy was performed. The patient subsequently appeared before an appellate court that found E.G. to be a competent, "mature" minor, capable of making her own decisions and, therefore, possessing the right to refuse further transfusions. The Supreme Court of Illinois reaffirmed this decision and also ordered that the finding of neglect against the mother be expunged.

It is unclear whether the legal morass will ever offer definitive guidelines to physicians caring for patients who refuse aspects of medical therapy and choose, perhaps, to die. For the first time, however, the US Supreme Court appears ready to hand down a decision in the first "right to die" case to appear before it.[13] The high court's decision will undoubtedly play a major role in future decisions regarding Jehovah's Witnesses.

ETHICAL CONCERNS

An understanding of the religion and legal doctrine aside, the ethical problems posed by the Jehovah's Witnesses' refusal of transfusion continue to trouble hospital administrators and physicians alike. It is not necessarily assured that an open doctor-patient relationship will minimize, if not eliminate, these concerns, as exemplified in *Brooks*. Jehovah's Witnesses will, however, actively seek treatment from hospitals and physicians who are sympathetic to their needs and who they feel will honor their wishes even in the face of dire circumstances.[16] In a similar regard, institutions and/or professional staff may, from the onset, refuse to accept responsibility for the care of the Jehovah's Witness patient, deciding instead to refer the patient to another hospital or physician. However, when a physician assumes the responsibility of care for the Jehovah's Witness, all possible alternatives to transfusion should be discussed with the patient and clearly defined in the medical record. As previously mentioned, each Jehovah's Witness may interpret their faith's teachings in different ways; therefore, it behooves all physicians to document which forms of therapy are acceptable to the patient. Regardless of the clinical situation (emergency versus elective) or the type of patient (minor versus adult; competent versus incompetent), a refusal of consent for transfusion form should be signed, if possible, by both the patient and his or her nearest relative. This waiver is binding on the patient (or the patient's estate) and offers protection for the physician in the event of a malpractice claim for failure to transfuse. Indeed, it has been stated that liability for failure to forcibly transfuse an unwilling patient "seems more the product of a fertile legal mind than a realistic possibility."[44]

Ultimately, it comes down to the clinical judgment of individual physicians or concurring physicians to decide when a patient requires a transfusion in order to sustain life. Regardless of whether the patient is a Jehovah's Witness, this is a decision that, in this modern era, can no longer be dealt with in a cavalier manner. Gone are the days of transfusing a patient preoperatively to the "magic" number of 10 g of hemoglobin.[11] Prophylactic platelet transfusions based on the number of previously administered RBC units is no longer considered standard of care, and plasma transfusions are essentially indicated only in the setting of a coagulopathy.[1] Certainly, a major concern of transfusion relates to the transmission of virally mediated diseases. The incidence of non-A, non-B hepatitis from a transfusion may be ≤1 in 100/U transfused, and that of hepatitis B may still be 1 in 200/U to 1 in 300/U.[11] The risk of contracting HIV from a transfusion may be in the range of 1 in 40,000/U to 1 in 100,000/U.[11] It is this risk that may have many non-Jehovah's Witnesses refusing to consent to perioperative transfusions for their elective surgeries.

In the perioperative setting, the ethical dilemma involves not only the surgeon but the anesthesiologist as well. Anesthesiologists are often at the forefront of emergency transfusion care, being in the position to "save a life by a simple twist of the wrist."[34] Yet, this potentially life-saving maneuver is limited by the informed refusal of the patient and the surgeon's acceptance of the patient's desire to die rather than accept a transfusion. It is imperative, therefore, that an anesthesiologist with knowledge and expertise in techniques that limit intraoperative blood loss be part of the initial discussions with both the patient and the surgeon. What about the anesthesiologist who, for his or her own religious or personal beliefs, refuses to be involved in the care of a patient who puts restraints upon his or her practice? It is obvious that mechanisms need to be in place to insure that qualified personnel will be available to meet the demands of the Jehovah's Witness patient. In the emergency situation, when no time is available for consultation with patient or family, most physicians would be inclined to institute transfusion therapy if the patient's life were at stake. This ethical decision would be universally supported in the courts, although it must be emphasized that legal counsel should be obtained as early as possible in this situation.

Finally, many ethical questions remain difficult to answer. In the setting of a minor, is it best to seek a court order and transfuse against the will of both the child and the parent? Does this approach constitute "paternalism," and does it outweigh the patient's right to obtain what Jehovah's Witnesses consider eternal life?[34] It is apparent that these questions can only be answered by the individual physician based on his or her own moral and ethical beliefs.

THE MEDICAL APPROACH TO THE JEHOVAH'S WITNESS PATIENT

Having entered into the care for the Jehovah's Witness patient, it is important that the physician be acquainted with available techniques to limit intraoperative blood loss and with non-blood–containing solutions that tend to be acceptable forms of therapy to these patients. Table 1 lists many of these alternative therapeutic modalities. The reader is referred to other sections of this text, as well as other excellent reviews,[5] for a more detailed description of each individual technique or therapy. Table 2 lists procedures that are potentially acceptable to the Jehovah's Witness patient. Many major surgical procedures have been performed successfully in Jehovah's Witnesses without the need for blood transfusion. These surgeries include major abdominal procedures, including renal transplantation[37, 39]; major obstetric and gynecologic procedures, including cesarean section[6];

Table 1. *Perioperative Alternatives to Blood Transfusions*

ACCEPTABLE TO THE JEHOVAH'S WITNESS	POTENTIALLY ACCEPTABLE	UNACCEPTABLE*
Crystalloid solutions	Extracorporeal circulation (nonblood-primed)	Component therapy
Synthetic colloid solutions	Hemodilution	Autologous blood
Dextran	Human albumin	
Perfluorocarbons	Cell-saver systems	
Hypotensive anesthesia		
Induced hypothermia		
Erythropoietin		
Desmopressin (DDAVP)		
Iron		

* Should be discussed with the individual patient; some may accept these forms of therapy.

major orthopedic procedures, such as total hip arthroplasty[7, 41] and spinal fusion[8, 58]; and open-heart surgery, including coronary artery bypass[43] and heart transplantation.[12] Despite the fact that deaths have occurred in the perioperative setting due to massive hemorrhage,[20, 43] the overall operative mortality has not been found to be statistically different when comparing Jehovah's Witnesses with the general population.[14]

CONCLUSION

Physicians whose patient population may include members of the Jehovah's Witness faith must realize that their patients truly believe that receiving a transfusion will prevent them from ever attaining eternal life after death. Jehovah's Witnesses are not suicidal, but neither are they likely to be willing to accept a transfusion in order to avoid death. When these patients clearly need transfusions, the caring physician is faced with the challenge of balancing the patient's apparent First Amendment right against the physician's duty to administer the highest quality medical care. Under certain circumstances, the physician may seek legal authorization to transfuse a Jehovah's Witness

Table 2. *Potentially Acceptable Procedures to the Jehovah's Witness Patient*

Organ donation/transplantation
Immunization/vaccination
Epidural blood patch

despite the patient's religious convictions. In the absence of legislation dealing with the refusal of therapy, the physician and the courts are left to rely solely on the precedents of case law. Physicians, particularly anesthesiologists, need to develop a decision-making process before they agree to care for Jehovah's Witness patients. Such a process should be based on each physician's individual ethical beliefs, coupled with his or her clinical expertise in alternate transfusion practices.

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A Commentary on Three Consensus Development Conferences on Transfusion Medicine

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In partial response to the perception that a long lag time existed between the development of a new technology or information on a well-established therapeutic modality and the clinical application of the same, Consensus Development Conferences (CDCs) were developed by the National Institutes of Health (NIH) Office of Medical Applications of Research. These conferences have been held on a wide variety of subjects, but none has had implications for anesthesia practice equivalent to the CDCs' on fresh frozen plasma (FFP), platelet transfusion therapy, and perioperative red blood cell (RBC) transfusion.[3–5]

The administration of blood products to patients may be the most common therapeutic maneuver performed by anesthesiologists that is not related to the relief of pain. In the past decade, there have been numerous developments in transfusion medicine that have affected the way in which this therapeutic maneuver is performed. The recognition that acquired immunodeficiency syndrome (AIDS) can be transmitted by a blood transfusion has been a strong force for the increasingly conservative approach to homologous blood transfusion. Likewise, increased fractionation of whole blood into its components has undoubtedly had a profound impact on the intraoperative practice of transfusion medicine. Figure 1 illustrates these developments from one institution.

In response to these developments and the concern that blood components may not always be used appropriately, three CDCs (Table

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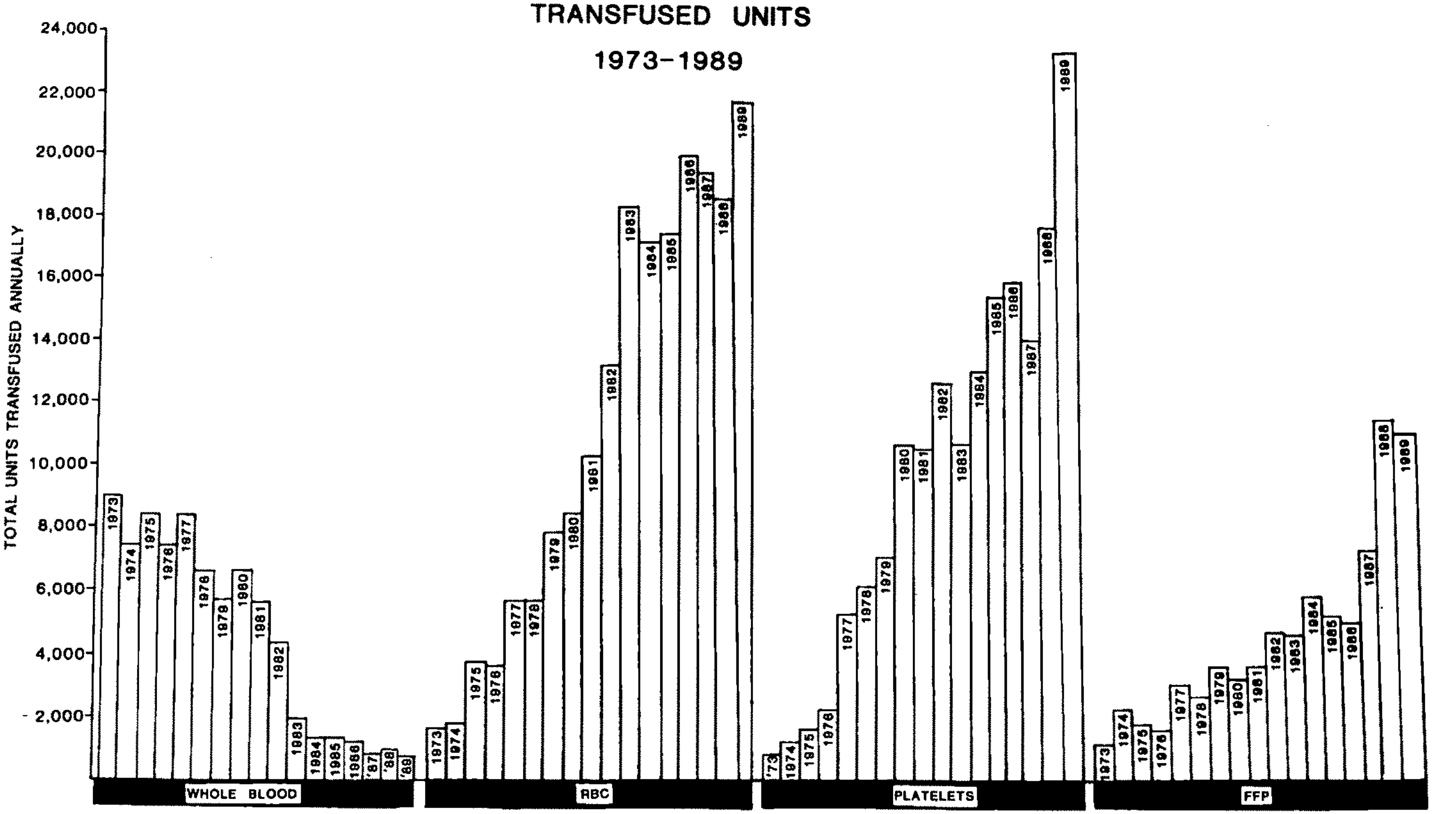

Figure 1. Blood transfusion practices over a 16-year period at the Hospital of the University of Pennsylvania. These practices mirror the nationwide move toward the disappearance of whole blood, the increased use of blood products with twice as much RBC transfused in 1989 as whole blood and RBC combined in 1973, and the exponential increase in the use of platelets and fresh frozen plasma.

Table 1. *Consensus Development Conferences Regarding Transfusion Medicine*

MEETING	DATES	PUBLICATION	ANESTHESIOLOGIST ON PANEL
Fresh frozen plasma	Sept 24–26, 1984	JAMA 253:551–553 (Jan 25), 1985	Ronald D. Miller, MD
Platelet transfusion therapy	Oct 6–8, 1986	JAMA 257:1777–1780, (April 3) 1987	Linda C. Stehling, MD
Perioperative RBC transfusion	June 27–29, 1988	JAMA 260:2700–2703 (Nov 11), 1988	David E. Longnecker, MD

1) have been held at NIH to review the available information on those components, to suggest guidelines for their use, and to indicate what directions future research should take. In each conference a carefully selected panel drawn from several medical specialties, blood banking organizations, and the general public heard testimony for 1.5 days and then issued a report.

In this article much of the material presented will be in direct quotes or condensations of the final report. Italicized statements are commentaries of the authors regarding the CDCs, other readings, and their personal biases.

FRESH FROZEN PLASMA

Fresh frozen plasma is the acellular portion of 1 U of blood that has been centrifuged, separated, and frozen solid at −18°C (or colder) within 6 hours of collection. In response to the tenfold increase in the use of FFP in the preceding decade to over 1 million U/yr, a CDC was held in 1984. Five questions were addressed (Table 2).

In the introductory remarks at the CDC, the chairman stated that:

> The widespread use of fresh frozen plasma is attributable in part to its myriad constituents. It contains all of the proteins that modulate immunity, the proteins that maintain colloid oncotic pressure, the proteins of the coagulation cascade, and di-

Table 2. *Questions Addressed to the Panel on Fresh Frozen Plasma*

What are the currently recommended clinical indications for FFP?
What are the risks of FFP?
What alternative therapy exists?
What is the current scientific knowledge regarding the effectiveness of FFP?
What directions for future research are indicated?

> verse trace components, such as hormones, enzymes, and metal-binding proteins. Knowledge of this content has led clinicians to employ fresh frozen plasma as a therapeutic agent in a wide range of clinical disorders without clearly defined specifications. These disorders include shock, volume replacement, hypogammaglobulinemia, burns, sepsis, diffuse intravascular coagulopathy (DIC), liver disease, and nutritional supplementation.

Throughout the conference and the in final report it was mentioned that, in many cases, specific indications for FFP administration were lacking, except for the treatment of deficiencies of those procoagulants for which specific factor concentrates are also lacking. The widespread use of FFP in the uncontrollable bleeding patient was cited as an example; despite the strongly held belief of many clinicians in the therapeutic value of FFP, data supporting its efficacy are lacking. The CDC went on to acknowledge that such patients were often critically ill and, in the absence of alternative therapy, "FFP may be appropriate." *Additionally, the lack of supportive data probably reflects the difficulty in collecting the same in this patient population.*

Fresh frozen plasma contains the two labile factors, V and VIII, which are not present in single-donor plasma. Because there are specific products, cryoprecipitate or factor VIII concentrate, available to treat factor VIII deficiency, FFP is used to treat factor V deficiency specifically. There are three other single-donor plasma products that can be used interchangeably with FFP in cases other than factor V deficiency. These three products are (1) plasma not frozen immediately after fractionation, (2) FFP used 1 year after collection, and (3) cryoprecipitate-poor plasma.

What Are the Currently Recommended Clinical Indications for FFP?

Replacement of Factors II, V, VII, IX, X, and XI. Because only 5% of factor V and 10% of factor X are required for effective hemostasis, these levels can be readily achieved with the administration of FFP. However, symptomatic deficiencies of these two factors rarely occur in the surgical setting. Conversely, achieving hemostatic levels of factor IX in a patient with a severe deficiency is difficult to accomplish using FFP. Furthermore, there is a specific concentrate available for the treatment of factor IX deficiency. Unfortunately, as a pooled product, the concentrate carries a high risk of transfusion-associated disease.

Reversal of Warfarin Effect. Production of the vitamin-K–dependent factors II, VII, IX, and X (prothrombin complex) is inhibited by warfarin. To restore normal prothrombin time by withholding the drug may take over 24 hours, depending on the commercial product used and the level of inhibition that must be neutralized. The administration of vitamin K can reduce this time period to 4 to 6 hours in the presence of normal liver function when starting with a prothrombin time in the therapeutic range of 2.0 to 2.5 times normal. *These two therapeutic maneuvers are preferable to the use of FFP, which should be used only in cases of active bleeding or emergency surgery where immediate neutralization of the warfarin effect is necessary.* The other three single-donor plasma products previously mentioned, which are deficient in factors V and VIII, are equally effective as FFP in such cases.

Massive Blood Transfusion (Greater Than One Blood Volume Within Several Hours). "Use of FFP in massive blood transfusions, for which there is less credible evidence of efficacy, appears to be increasing in frequency in the past decade, possibly due in part to the relative unavailability of whole blood." However, a dilutional thrombocytopenia is more likely to be the cause of bleeding in these patients. As mentioned previously, documentation of the therapeutic effects in treating the uncontrollable bleeding patient is lacking. Although prophylactic use of FFP has never been demonstrated to be of value, the administration of multiple units of RBCs in this era of 80% or more fractionation of whole blood, especially now that ADSOL has replaced CPD as the additive, does present the theoretical potential of decreasing all factor levels below hemostatic levels. The use of "modified whole blood," from which platelets and factor VIII have been removed, is another proposal to solve this problem.[6] As indicated previously, both the volume administered and the rate of the administration must be considered, because production of the coagulation factors will be ongoing and may keep pace with slow losses.

Use in Antithrombin III Deficiency. Fresh frozen plasma administration "to patients who are deficient in this inhibitor and are undergoing surgery or who require heparin for treatment of thrombosis" is indicated.

Treatment of Immunodeficiencies. Purified immune globulin for intravenous use has largely replaced FFP. However, "in infants with secondary immunodeficiency associated with severe protein-losing enteropathy in whom total parenteral nutrition is ineffectual," FFP is useful. Fresh frozen plasma *is also useful in patients who have had an anaphylactoid reaction to IgG.*

Treatment of Thrombotic Thrombocytopenic Purpura. "FFP may be beneficial for the treatment" of this condition.

Fresh Frozen Plasma

"The risk[s] of FFP include disease transmission, anaphylactoid reaction, alloimmunization, and excessive intravascular volume." The potential for disease transmission is the same as for whole blood and RBCs and depends on many factors, especially donor selection, with the incidence of nonicteric and icteric hepatitis ranging between 3% and 10%. (This CDC was held shortly after the first publication describing transfusion-associated AIDS and was very specific regarding the low probability of transmitting AIDS via FFP.) "In rare instances acquired immunodeficiency syndrome is transmitted by blood transfusions and possibly by FFP." An allergic or anaphylactoid reaction can occur in response to FFP administration and may vary from hives to fatal noncardiogenic pulmonary edema.

What Alternative Therapeutic Methods Exist?

"Other plasma components (e.g., single-donor plasma) that do not meet criteria for FFP may have adequate levels of coagulation factors and be suitable for patients in whom FFP is indicated." In this report the call for blood conservation, especially for autologous blood transfusion, was mentioned and has been followed by several publications, culminating in the National Board Resource Education Program.[8, 11]

Single-donor plasma, which lacks only factors V and VIII, can be used to treat deficiency of stable factors, especially warfarin-induced depression of the prothrombin complex. Cryoprecipitate and factor VIII and IX concentrates are now available to treat specific deficiencies, although the concentrates, being prepared from pooled plasma, carry a high risk of disease transmission. Factor IX concentrate carries the additional hazard of thrombogenicity.

The use of FFP as a volume replacement was especially condemned, and crystalloid, colloid, (albumin or plasma protein fraction), hydroxyethyl starch, and dextran were mentioned as substitutes. *Again, the issue of administering RBC and FFP in lieu of whole blood was cited as increasing cost and doubling the infection rate exposure.*

Current Scientific Knowledge Regarding the Effectiveness of Fresh Frozen Plasma

"There is little scientific evidence to support the increasing use of FFP in clinical medicine." Although this statement may seem contradictory, in view of the several specific indications previously listed, the tenfold increase in FFP over the past decade is believed in large measure due to use in the bleeding patient receiving massive transfusion. A review article published just prior to the CDC on FFP came to the same conclusion and offered only several broad guidelines to govern administration of FFP in these patients (Table 3).[2]

Directions for Future Research

Several goals for future research are listed in Table 4.

Summary

The panel report concluded that FFP use is controlled locally and is determined by existing practice. *In that regard, an analysis of regional, hospital, and even specific physician variations as part of the suggested national prospective study would be of interest.* Swisher[12] characterized the lack of indications as "an indictment of the past and current education practices for both medical students and residents in the area of transfusion medicine." The report concluded with a call for "innovative educational efforts to encourage appropriate use."

Table 3. *Guidelines for Fresh Frozen Plasma Use in Massive Transfusion*

The initial volume required for significant effect on the coagulation status needs to be large and administered rapidly, such as 600–2000 mL over 1–2 h

There is probably no indication for FFP administration to patients with severe liver disease and abnormal levels of coagulation factors who are not actively bleeding or facing a hemostatic challenge. (Any surgical procedure may be considered a hemostatic challenge)

FFP is not likely to help trauma and postoperative patients who are not actively bleeding or patients undergoing elective operations with moderate blood replacement unassociated with shock

FFP may help control abnormal bleeding in trauma patients receiving massive transfusion. Again, large volumes rapidly administered are necessary. Particular attention to platelet levels is more important because a dilutional thrombocytopenia is a more common cause of bleeding in this setting

Although there is no shortage of set schedules for administration of FFP, most of which are unreferenced and anecdotal, not one regimen has proved effective

Rigid use of the activated partial thromboplastin time or prothrombin time to anticipate the probability of beneficial effect of FFP is not justified. Although these tests may help in individual cases, their poor predictive value for the development of abnormal bleeding diminishes their usefulness

Abstracted from Braunstein AH, Oberman HA: Transfusion of plasma components. Transfusion 24:281–285, 1984.

PLATELET TRANSFUSION THERAPY

The increase in platelet transfusions demonstrated in Figure 1 is merely a reflection of what has happened nationwide. This increased use has resulted in decreased deaths due to hemorrhage in patients with chronic thrombocytopenia and has permitted more aggressive

Table 4. *Recommendations for Future Research on Fresh Frozen Plasma*

A national prospective study to identify current patterns of use of FFP and related product

Better understanding of the balance between coagulation and fibrinolytic systems, their activators and inhibitors, and their roles in the coagulopathies associated with liver disease in massive transfusion

Definition of the etiology of uncontrollable hemorrhage in the patient receiving massive transfusion

Clinical investigations to identify the factor(s) in FFP that appears to cause beneficial effects in patients who are undergoing aphereses for treatment of syndromes such as thrombotic thrombocytopenia purpura

Blood and plasma salvage during operative procedure

Production of the safest possible specific plasma constituents and substitute

Processes or method to eliminate or inactivate viral or bacterial contaminants

Technology involving membrane-separation techniques to separate cellular products more efficiently

Development of an efficient system by which a larger volume of FFP can be collected from a single donation, thus reducing the number of donor exposures in a single recipient

Table 5. *Questions Addressed to the Panel on Platelet Transfusion Therapy*

What are the appropriate indications for platelet transfusion?
What products are available, and what are their relative merits?
What are the risks associated with platelet transfusion?
What are the most important directions for future research?

therapy with drugs that temporarily suppress platelet function in oncology patients. To resolve issues ranging from disease transmission and prophylactic use to collection and storage of platelets, a CDC was held to answer four questions (Table 5).

What Are the Appropriate Indications for Platelet Transfusion?

Concern was expressed in the report that platelets were administered (1) to patients who did not need them, (2) too frequently to patients who did need them; and (3) occasionally in insufficient quantities to those who did need them. The lack of properly controlled trials, imprecise methods of evaluating clinical need, and uncertain methods for measuring the effect have all hampered clinical decisions regarding platelet transfusion. Platelet levels below which patients are at risk for hemorrhage and the efficacy of other treatment therapies are not well defined. Other factors such as medication, concomitant coagulation disorders, and disease state (e.g., uremia) will also alter the efficacy of platelet transfusion.

Active Bleeding. "Patients with thrombocytopenia or an abnormality of platelet function who have significant bleeding should receive platelets if the platelet disorder is likely to be causing or contributing to the bleeding." *Although the report acknowledges the difficulty in making this judgement clinically, one method is therapeutic trial. In the presence of documented thrombocytopenia or abnormal platelet function withholding platelet transfusions seems unwarranted.* Specifically, platelet counts of 50,000/mm^3 or bleeding times less than twice normal are mentioned as cutoffs for the use of platelet transfusion. Thrombocytopenia secondary to increased antibody-mediated destruction is generally not treated with platelet transfusion.

Prophylaxis. Patients with severe thrombocytopenia may benefit from prophylactic treatment, especially if the decrease is secondary to myelosuppresive therapy. While 20,000 platelet/mm^3 is often used in such cases, the report suggests that a lower level may be safe. The lack of reproducibility and the variability of platelet counts at such low levels makes any specific cutoff recommendation difficult. Patients with chronic thrombocytopenia secondary to impaired platelet production (e.g., aplastic anemia or myelodysplastic disorders) generally do not require platelet transfusion. Those patients with increased destruction with active production (e.g., idiopathic thrombocytopenic purpura) have less bleeding at a given platelet level than patients with hypoplastic platelet disorders, and therefore, platelets are rarely used in the former.

"Preparation for invasive procedures in thrombocytopenic or thrombocytopathic patients might include prophylactic administration of platelets," *and any surgical procedure is invasive*! This is especially true in patients for whom hemostasis can not be assessed by direct observation. Again, pertinent studies on which to base practice are lacking. Similarly, patients threatened with central nervous system hemorrhage, where a small amount of bleeding can be critical, may benefit from prophylactic platelet therapy.

Massive Transfusion. "Dilutional thrombocytopenia occurs in patients receiving multiple transfusion to replace blood loss through hemorrhage and may lead to generalized microvascular bleeding." A single blood volume replacement will leave 35% to 40% of platelets, but a smaller percentage may remain in the presence of accelerated platelet destruction superimposed on a single blood volume exchange. *Accordingly, platelet counts must be used to guide therapy, and serial platelet counts are often necessary.* Microvascular bleeding secondary to thrombocytopenia rarely occurs with a one- or two-blood volume replacement. Thus, both documented thrombocytopenia and clinically abnormal bleeding should be present before platelet transfusion in this patient population.

Cardiac Surgery. *Some degree of platelet dysfunction, presumably due to the heart-lung machine, as well as a decrease in platelet count, is a consistent finding in patients following cardiopulmonary bypass.*[7] However, many studies have documented the lack of correlation between platelet count and bleeding, and the prophylactic use of platelet transfusions has *never* shown any detectable benefit. The report states, "With an expected pattern of bleeding, thrombocytopenia alone is not an indication for platelet transfusion." *However, if the platelet count is less than 100,000 platelets/mm^3, few clinicians would feel that withholding platelet transfusion would be justified in the presence of an unusual bleeding pattern.*

Newborns. No specific comments were made other than to avoid undue exposure to multiple-donor sources.

What Products Are Available and What Are Their Relative Merits?

Multiple-donor or single-donor platelets in which the platelets are obtained by an apheresis from a single-donor (approximately equivalent to 5 to 8 whole blood donations) are available. Single-donor platelets can be randomly obtained on the basis of HLA compatibility. Product availability as well as the potential for disease transmission and alloimmunization clearly influence local practice.

Products. The obvious advantage of single-donor platelets is the decreased risk of disease transmission and alloimmunization. However, there is no evidence of increased efficacy in patients who have not been alloimmunized. The major advantage of multiple-donor platelets is their relatively abundant supply. An added advantage is the 5-day shelf life versus the usual 24-hour limit for single-donor platelets.

In patients who become refractory to unselected single-donor platelets or multiple-donor platelets, HLA-matched single-donor platelets are the most effective. The greater donor commitment and equipment complexity for this product dictate a restricted use.

Storage. Platelets stored at 4.0°C are rarely used because of decreased survival and dysfunction after transfusion. Storage at 20°C to 24°C with constant agitation for 5 days is the current practice. Cyropreservation can extend the storage period. Storage of autologous platelets during remission for latter use during aggressive chemotherapy-induced hypoplasia following a relapse is especially indicated.

Dosage. A dose of 1 U/10 kg of body weight or one single-donor platelet product is a common starting point. Clinical observation of decreased bleeding and platelet count 1 hour after transfusion will permit the efficacy of platelet transfusion to be monitored and will provide guidance for further therapy. A standard 150-μm filter is recommended for transfusion, and smaller filters are not indicated.

Adjunctive therapy. Cryoprecipitate or desmopressin acetate may stop bleeding in the uremic patient, thus avoiding platelet transfusion. *The use of cryoprecipitate, however, will expose the patient to another blood product and, possibly, to the same number of donors.* ε-aminocaproic acid and desmopressin acetate have been used, but data to support regular use are lacking.

What Are the Risks Associated With Platelet Transfusion?

Alloimmunization and the Refractory State. "When platelet-reactive antibodies are induced by transfusion, platelets subsequently administered often fail to produce a therapeutic benefit." It is not clear why an appreciable number of patients fail to form platelet-reactive antibodies, for there is no relationship between the number of donor exposures and the extent of antibody formation. Alloimmunization to HLA-A and HLA-B is encountered most frequently and leukocytes, invariably present in platelet concentrates, provoke HLA-antibody formation more readily than platelets. When HLA-matched platelets fail to increase the platelet count after transfusion in some alloimmunized patients, another mechanism for platelet destruction must be active, and that may be a non-HLA-platelet–specific antigen. The administration of HLA-matched platelets to alloimmunized patients is effective in only two thirds of patients. High-dose IV gamma globulin, splenectomy, and plasmapheresis to remove platelet alloantibotidies have been marginally effective.

ABO compatibility is of minor importance in platelet transfusion treatment in most adults. Rh immunization in the premenopausal female by RBCs present in the platelet concentrate must be considered.

Infection. Although this risk is similar to the other blood products, the risks are of special concern because platelet transfusions are often prepared from multiple donors and administered in large numbers to

Table 6. *Recommendations for Future Research in Platelet Transfusion Therapy*

- Recipient-related issues
  - Development of a practical test that predicts the likelihood of clinically significant platelet-related bleeding
  - Controlled clinical trials to evaluate strategies for prophylactic use of platelets in patients with disorders of platelet productions
  - Evaluation of pharmacologic approaches designed to reduce platelet requirements
- Product-related issues
  - Development of better techniques to harvest platelets with minimum contamination with other blood components
  - Better methods of platelet preservation
  - Practical means for detecting ineffective units and bacterial contamination prior to transfusion
  - Better characterization of platelet alloantigens and the development of practical methods to detect alloantibodies and select compatible donors
  - Effective means to prevent alloimmunization and to treat the alloimmunized patient
  - Development of methods and strategies to lessen the instance of transfusion-transmitted diseases
  - Monitoring of the patterns of platelet use
- Donor-related issues
  - Assessment of long-term effect of repeated platelet apheresis
  - Identification of factors leading to successful recruitment of platelet-apheresis donors

immunocompromised patients. A rare complication of platelet transfusion that may be fatal is the infusion of bacteria that have proliferated during storage at 20°C to 24°C. Aggressive treatment with antibiotics and supportive measures is required to treat these patients.

Graft versus Host Disease. "Graft-vs-host disease is a rare complication of platelet transfusion that can be prevented by gamma irradiation of concentrates prior to transfusion to patients who have undergone bone marrow transplantation or have other forms of immunodeficiencies."

What Are the Most Important Directions for Future Research?

The several goals for research are listed in Table 6.

Summary

This report expressed the belief that platelets are overused in some conditions and specifically cited prophylactic use in cardiac surgery as an example. In the clinical area, the lack of methods for predicting which patients are at risk for bleeding and the effectiveness of various platelet preparations prompted a call for research initiatives to provide better guidelines for transfusion practice. In the basic science area, research to elucidate the role of platelets in hemostasis and to overcome the problems associated with alloimmunization to platelets is needed. A surveillance system at the national level as well as a national network to facilitate transfusion of HLA-matched platelets to selected patients was called for. In addition to concern of disease transmission associated with all blood products, the elimination of bacterial growth in platelet concentrates stored at room temperature warrants special attention.

PERIOPERATIVE RED BLOOD CELL TRANSFUSION

A reexamination of the risk-benefit ratio for RBC transfusion therapy was deemed appropriate in light of the apprehension regarding transmission of infectious disease associated with transfusion. *In contrast with platelet transfusion, where oncologic patients receiving chemotherapy are the principal users,* approximately 67% of RBC transfusions are administered in the perioperative period. The conference was designed to answer five questions (Table 7).

What Should Be the Criteria for Perioperative Red Blood Cell Transfusion?

The term "transfusion trigger" has been applied to the value at which a given physician chooses to transfuse a patient. A common "trigger," the so-called "magic number" of 10 g/dL hemoglobin or hematocrit of 30%, has long been a guide to transfusion therapy in the surgical patient. This number was the first challenged in the early 1960s as experience in treating severely anemic patients with chronic renal failure or other conditions accumulated. *Patients who are Jehovah's Witnesses and refuse blood transfusion on religious grounds also challenged physicians to treat patients without resorting to blood transfusion.* The accumulated experience indicated that severe anemia, per se, does not increase morbidity and mortality, refuting the "10/30" rule. *Although carefully controlled randomized trials addressing this issue are lacking, the available evidence would seem to make them unnecessary.* Indeed, Graves and Allen[9] wrote 15 years earlier

> The time honored limit of 10 grams of hemoglobin seems to be based more on theory than clinical or experimental evidence. This limit is predicated on the assumption that during anesthesia when tissue oxygenation is dangerously critical, especially if the anesthetic techniques are flawed, one should therefore transfuse preoperatively to increase the patient's margin of safety.

Cardiac output does not increase dramatically in healthy humans until

Table 7. *Questions Addressed to the Panel on Perioperative Red Blood Cell Transfusion*

What should be the criteria for perioperative RBC transfusion?
What is the morbidity of anemia in the perioperative period?
What are the risks of RBC transfusion—both immediate and long-term?
What are the alternatives to RBC transfusion?
What are the directions of future research?

hemoglobin levels decrease to less than 7.0 g/dL, and anesthetized, paralyzed, ventilated animals may survive acute isovolemic anemia down to hematocrits of 5%. However, significant functional deterioration will occur well before that value.

> The decision to transfuse a specific patient should take into consideration the duration of anemia, the intravascular volume, the extent of the operation, probability of massive blood loss, and the presence of existing conditions such as impaired pulmonary function, inadequate cardiac output, myocardial ischemia, cerebrovascular or peripheral circulatory disease. These factors are representative of the universe of considerations that comprise clinical judgment. . . . It is essential to recognize that the combination of hypovolemia and anemia may lead to severe morbidity and/or mortality and there is a minimum hemoglobin value for each individual, below which severe morbidity and/or mortality due to inadequate oxygen delivery is likely to occur.

In summary, the only indication for RBC transfusion is to increase oxygen-carrying capacity.

What Is the Morbidity of Anemia in the Perioperative Period?

"Any adverse effect that occurs immediately preceding, during, or after the operation is considered to be perioperative morbidity." Examples include wound infection, delayed wound healing, bleeding, and impaired recovery. Many clinicians and patients are concerned that anemia may increase perioperative morbidity. However, it must be recognized that anemia may be severe or mild, acute or chronic.

> It is important to separate the effects of hypovolemia and decreased perfusion from the effect of anemia. If there is normal intravascular volume and normal tissue perfusion there is no adverse effect in cardiovascular function until anemia is profound.
>
> Healing of surgical wounds depends on angiogenesis, collagen deposition, and epithelialization. There is no support for transfusion to a certain hemoglobin level or hematocrit to promote wound healing.

Similarly, there is no clinical evidence in anemic patients of increased bleeding during or after surgery.

What Are the Risks of Red Blood Cell Transfusion, Immediate and Long-term?

In each transfusion the need for possibly improving oxygenation must be weighed against the risk of adverse consequences, both short-term and long-term. Disease transmission and adverse effects attributable to immune mechanisms are among the risks.

Infection. Bacterial contamination of RBCs is rare, and essentially the only transmissible agents are viral. It is known that the incidence of human hepatitis virus infection increases with the number of donor exposures, and it is reasonable to assume that this applies to other diseases.

Human hepatitis virus is the most frequently transmitted infectious disease. With donor screening and nonspecific tests such as antibody to hepatitis B core antigen and alanine aminotransferase levels, the incidence of non-A, non-B infection may be 1 in 100 or less per unit. Despite a specific screening procedure for hepatitis B in existence since 1971, the incidence of infection is still in the range of 1 in 200 to 300.

Human immunodeficiency virus, which has caused the greatest public concern, poses a remote hazard due to donor selection and laboratory screening, with an estimated incidence of 1 in 40,000 to 1 in 1 million.

"Cytomegalovirus occurs with moderate frequency among these recipients without prior infection. Most of these infections are asymptomatic except among immunocompromised people."

"Human T-cell lympotrophic viruses occur with low but not negligible frequencies."

Hemolytic and Nonhemolytic Reactions. Hemolytic and nonhemolytic reactions secondary to alloimmunization to RBCs and white blood cell antigens occur. Immediate hemolytic reaction can be eliminated by compatibility testing. *This is fortunate, because these reactions, which can be fatal, are invariably secondary to human error.*[10] Nonhemolytic reactions occur in 1% to 2% of recipients secondary to white blood cell administration, and this incidence can be decreased with leukocyte-poor blood products. The incidence of fever, chills, and urticaria is 1 in 100; hemolytic transfusion reaction, 1 in 6000; and fatal hemolytic transfusion, 1 in 100,000.

What Are the Alternatives to Red Blood Cell Transfusion?

Although homologous red blood cell infusion has become continuously safer and is a major therapy, it should not be considered a substitute for good surgical and anesthetic techniques. Progress in anesthesia has allowed more time for the surgeon to be fastidious about hemostasis and new surgical techniques have approved the surgical ability to control bleeding.

Autologous Transfusion Program. Currently, 2% of transfusions are autologous, and it is anticipated that this number can be increased considerably. Toy et al[13] pointed out that only 5% of the potentially eligible patients were participating in a predeposit autologous program and that lack of patient participation is due to the apparent reluctance of physicians to refer their patients to these programs. "Clearly, something major is wrong if past attempts at communication with physicians and their patients have only resulted in 5% of the eligible patients participating."

Intraoperative Blood Salvage. This "seems to be safe in some applications and reduces the requirement for homologous transfusion."

Intraoperative Hemodilution. Selection of patients for intraoperative hemodilution is based on still-emerging criteria. Interestingly, the report distinguishes predeposit from scavenging and isovolemic hemodilution as other variants of autologous blood transfusion. Clearly, because all three result in the return of autologous cells to a patient, the designation of only predeposit as autologous would seem unduly restrictive.

Perfusion Maintenance. Maintenance of perfusion is still the primary problem in dealing with blood loss." The report mentions modified hemoglobin solutions and improved perflurochemical emulsions as possible future developments to support oxygen transport. The need to maintain normovolemia while tolerating decreased levels of hemoglobin must be emphasized in this context.

Pharmacology. "Pharmacologic approaches to reduce surgical blood loss are promising." Deliberate hypotension, a technique long known to anesthesiologists, and desmopressin were mentioned.

Recombinant Erythropoietin Therapy. "*Recombinant erythropoietin* therapy may be useful in avoiding homologous transfusion by increasing the amount of blood available in programs of autologous blood transfusion."

What Are the Directions of Future Research?

In calling for future research to "adhere to appropriate standards of research design, including adequate sample size, controls, multicenter sites, and randomization where feasible," the panel acknowledged the surprising lack of adequate studies on a subject of vital importance to the surgical patient. A similar call regarding the "magic 10/30" rule was made 20 years ago when Ballinger and Collins[1] stated that "anesthesia needs careful reevaluation of the hemoglobin level below which the administration of anesthesia is unsafe. The level is not the same for all patients nor for all operations." Specific areas of research are listed in Table 8.

Table 8. *Recommended Subjects for Future Research On Perioperative Red Blood Cell Transfusion*

The effect of anemia on the rate of recovery and length of hospital stay
The determination of the risk of transfusion-transmitted infection with contemporary donor screening procedures and evaluation of new measures to identify affected donors
The determination of immune changes induced by transfusion and their clinical consequences, if any
The identification of organs that are specifically at risk during acute anemia and the development of clinical monitors that measure directly and indirectly the state of perfusion and the presence of cellular hypoxia in those organs that are especially sensitive to low hemoglobin values
The development of predictors that better define the need for perioperative transfusion
The development of appropriate blood substitute
The performance of prospective controlled trials to evaluate the effects of increasing the hematocrit in anemic patients in the perioperative period
The evaluation and improvement of the safety and efficacy of autologous transfusion and intraoperative blood salvage procedures and the definition of criteria for selection of patients
The development of measures for the improvement of the safety of homologous blood transfusion
The evaluation of the risks and benefits of directed donation. The existing data are inconclusive

Summary

The panel's conclusions were specific, stating that the available evidence does not support the use of a single criterion such as 10 g/30% and that there is no evidence that mild to moderate anemia contributes to perioperative morbidity. Due to the risk of disease transmission and immune changes, homologous transfusion should be minimized. A variety of promising alternatives to homologous transfusion are being developed and will decrease the use of homologous blood products. "However, in the foreseeable future homologous blood transfusion will continue to be the therapeutic mainstay. . . Future research is necessary to define the best indications for red cell transfusion and the safest methods of blood conservation and delivery."

CONCLUSION

The three CDCs represent the collective opinion of experts drawn from several medical specialties, blood banking organizations, and the general public. Their conclusions were remarkable in that while they recognized unique areas such as bacterial contamination of platelets stored at room temperature, there were four common themes to the final reports:

1. Conservation is the most important way to avoid the risks associated with transfusion of blood products and every effort should be made to increase this practice, ranging from meticulous attention to hemostasis by surgeons to tolerance of lower hemoglobin level by anesthesiologists.
2. There is a surprising, even appalling, lack of adequate studies on the value of and indications for the blood products in question. *This lack is in contrast to the usual well-controlled studies that have accompanied the introduction of other therapeutic maneuvers.*
3. Educational efforts, to include at the local level strong proponents of modern transfusion practices to disseminate available data and current recommendations, are essential.
4. Future research is required to answer such basic questions as the role of platelets in hemostasis and the clinical indications for administering each of the three blood products in question.

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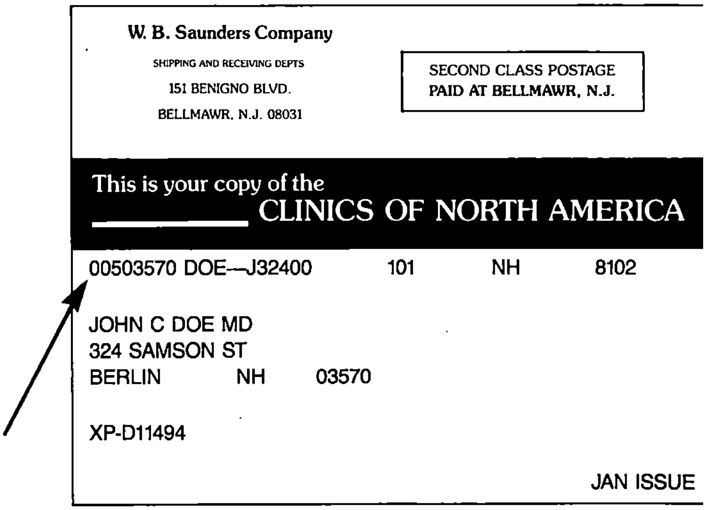

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